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ENDOCRINOLOGY

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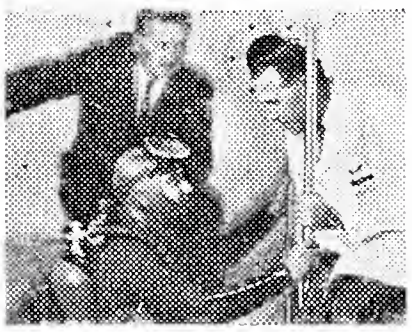

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Guest Editorial

J. C. LAIDLAW, M.A., M.D., Ph.D., F.R.C.P.(C)

Dr. Laidlaw graduated in 1942 in Biological and Medical Sciences, and in 1944 in Medicine, from the University of Toronto. He then became a rotating intern at the Toronto General Hospital. Following service in the Royal Canadian Navy, he received an M.A. in Biochemistry in 1947 from the University of Toronto, and a Ph.D. in the same subject in 1950 from the University of London. Following residency training in Medicine at the Toronto General Hospital, he spent three years in clinical investigation with Dr. George Thorn at the Peter Bent Brigham Hospital. In 1954 he returned to Toronto as a Markle Scholar on the staff of the Department of Medicine at the Toronto General Hospital. His practice has been in endocrinology, and his research has been in the field of adrenal cortical function in health and disease. Dr. Laidlaw is now Director of the Institute of Medical Science, Professor of Medicine, and Head of the Division of Endocrinology and Metabolism in the Department of Medicine at the Toronto General Hospital. He enjoyed immensely the work involved in his capacity as Co-ordinator of the Period II portion of the undergraduate medical curriculum from 1967 to 1971. He is married, and has two daughters, aged twelve and eight.

In no field of biology has there been as much ferment and excitement over the past forty years as in Endocrinology. Still youthful in 1971, Endocrinology in 1930 was barely in its infancy, with few of its hormones isolated, let alone characterized chemically. Since 1930 we have seen the isolation, identification of chemical structure, and in many instances synthesis, of a legion of hormones: thyroxine and triiodothyronine, calcitonin, parathormone, glucagon, a myriad of steroids from both the adrenal cortex and gonads, renin, angiotensin I and II, the prostaglandins, and even a number of the anterior pituitary polypeptides, growth hormone, ACTH and MSH. Much has been learned of the control of secretion of the target gland hormones, the circadian rhythm of their secretion, the nature of their transport in plasma via specific binding proteins, their metabolism and excretion.

In the present day there are three particularly exciting areas of development in Endocrinology: the control of secretion of anterior pituitary hormones, the mechanism of action of both pituitary trophic hormones and their target gland offspring at the cellular level, and the influence of hormones on behaviour. In the field of control of anterior pituitary hormone secretion, a series of specific releasing factors have been isolated from the hypothalamus. Two of these, thyrotrophin releasing factor (TRF) and luteinizing hormone releasing factor (LHRF) have been characterized chemically as small peptides, and synthesized. Of further interest is the evidence that brain catecholamines may play a role in the control of secretion of a number of these anterior pituitary hormone releasing factors.

The area of mechanism of action of hormones at the cellular level is being subjected to intensive study. It has now become clear for a number of hormones that their cellular action involves first an attachment to a specific receptor and thereafter stimulation of the production of the "second messenger" cyclic AMP.

Studies on the effects of hormones on behaviour show particular promise in two areas: the influence of male and female sex hormones on sexual behaviour, and the role of catecholamines in behavioural disorders. Development in the latter area is in its infancy. In the former area however, progress has been rapid, and profound changes in sexual behaviour have been observed in animals when minute amounts of sex hormones have been applied directly to specific areas of the hypothalamus.

GUEST EDITORIAL

In elinieal endoerinology it has been assumed that most alterations in the biological aetivity of hormones are due to inerease or deerease in the seeretion of these substances. It is now possible with a number of target gland hormones to measure ehanges in their secretion directly by means of rather complex isotopic techniques. In most centres however, relianee must be plaeed on indireet methods (determination of eoncentrations of hormones and their metabolites in plasma and urine) for detecting alterations in hormone produetion. Considerable improvement in the speeificity and sensitivity of these indirect procedures has been aehieved with isotopie techniques, particularly radioimmunoassay. Furthermore, the use of pituitary trophie hormones, and even releasing faetors such as TRF, along with measurement of hormone coneentrations in plasma and urine (the ACTH stimulation test, the TRF stimulation test) have greatly improved preeision of diagnosis of endoerine diseases. The latter test has recently disclosed a type of hypothyroidism due to a defieiency of thyrotrophin releasing faetor. While it is clear that our ability to detect alterations in hormone seeretion has improved immensely, it is now realised that the biologieal activity of hormones may be influeneed by ehanges in the disposition of hormones as well as by ehanges in the eellular milieu in which they aet. Our understanding of the role of these faetors is just beginning. Finally, delineation of the various lesions whieh may eause endoerine disease has been aided by the development of a number of radiological teehniques, e.g. renal arteriography, and the use of I^{131}-labelled eholesterol, for the detection of adrenal tumours.

The synthesis of many of the naturally-oceurring target gland hormones and their analogues has not only provided satisfaetory treatment for defieieney syndromes, but has also led to the successful use of pharmacologieal doses of a number of these hormones, e.g. glucocorticoids and sex steroids, in a variety of non-endocrine disorders. The reeent synthesis of growth hormone, and the finding that thyrotrophin releasing faetor is aetive by mouth, may well be forerunners of further exeiting advanees in the therapy of endocrine diseases.

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Prostaglandins

Robert W. Wald, B.Sc., Meds 7T2

INTRODUCTION

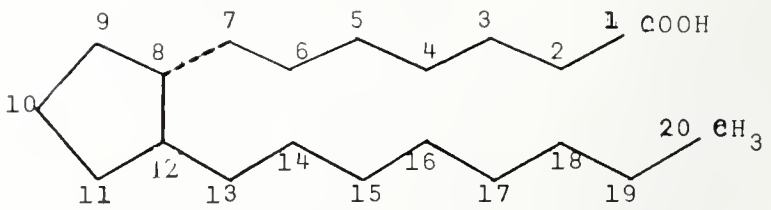
In 1930, two New York gynecologists, Kurzrok and Lieb, observed that the human uterus could react with strong contractions or relaxation on instillation of fresh human semen. During the first half of that decade, Goldblatt in England and von Euler in Sweden independently undertook the study of smooth-muscle stimulating activity of human seminal plasma and of extracts of the sheep vesicular gland.

"The ether- and water-soluble substance, which has the effects of lowering the blood pressure and stimulating various isolated smooth-muscle organs is provisionally named prostaglandin". Thus did von Euler coin the name for this new biologically active principle after having extracted it from sheep vesicular glands and identified it as an unsaturated fatty acid derivative different in character from any other biologically active compound known to that time. In retrospect, judging from the volume of ensuing investigative work, the original impact of prostaglandins upon the world of experimental biology was quite minimal.

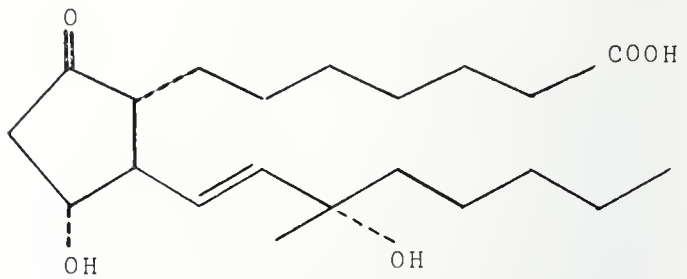
It was not until the late 1950's that interest in the study of prostaglandins (PGs) was sparked by their chemical identification and increased availability in research quantities. Using a non-specific but very sensitive bioassay utilizing the smooth muscle stimulating activity of PGs on rabbit duodenum, Bergstrom and Sjovall isolated two active crystalline compounds from extracts of sheep seminal vesicles. These were designated prostaglandin E_1 (PGE_1) and prostaglandin $F_1\alpha$ ($PGF_1\alpha$). Using gas chromatographic, x-ray diffraction and mass spectroscopy techniques they determined their chemical structure. Shortly afterwards, Bergstrom and Sammuelsson isolated and characterized a whole family of PGs.

There are 14 naturally occurring PGs of known structure, thirteen of which have been found in human semen. All are derivatives of the parent compound prostanoic acid, a twenty carbon monocarboxylic acid containing a cyclopentane ring (Fig. 1). The various prostaglandins differ in their nomenclature by the substituents on the parent structure represented in their nomenclature by the letter A or B (oxygen), E (oxygen and hydroxyl) and F (two hydroxyl groups) and by the number of double bonds, represented in their nomenclature by the subscripts 1, 2 and 3. In addition there are two possible stereoisomeric configurations for the PGF compounds. These are reflected in the nomenclature by the subscripts α or β. Only the α isomers are known to occur naturally. Of the fourteen naturally occurring PGs, six (the three PGEs and three PGFs) are considered to be primary, the rest being derived from these. Fig. 1 illustrates the structure of some of the PGs.

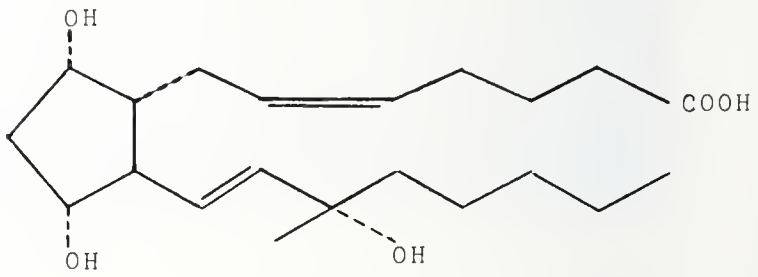
From the chemical structure of the PGs it became apparent that the unsaturated fatty acids referred to in nutrition as the essential fatty acids might serve as their biosynthetic precursors. One of these, linolenic acid, serves as a precursor to three others: γ-linolenic, dihomo-γ-linolenic and arachidonic acids. The latter two of these have been shown to be precursors to the pairs PGE_1 and $PGF_1\alpha$ and PGE_2 and $PGF_2\alpha$ respectively. The biosynthesis using vesicular gland homogenates yields mainly PGE compounds, whereas lung homogenates yield comparable amounts of F and E compounds, the proportion of which can be varied by controlling the amount and nature of added cofactors. No direct interconversion of E and F compounds has yet been observed. *In vitro* biosynthesis provided for the first time amounts of PGs adequate for widespread biological investigations. It is likely that total chemical synthesis will become the preferred source in the future.



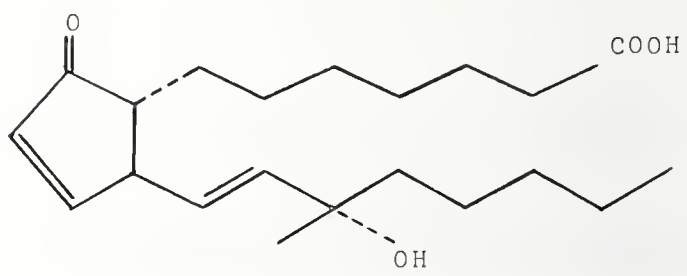
PROSTANOIC ACID



PGE_1



$PGF_{2\alpha}$



PGA_1

Fig. 1 Prostanoic acid, the parent compound and three representative PGs.

It is known that in rats, the absence of essential fatty acids from the diet results in symptoms of deficiency manifested by poor growth, skin lesions, kidney damage and impaired fertility. In children, certain skin lesions ascribed to this type of deficiency have been cured by administration of linoleate. Very little is known about the underlying mechanism and attempts to relieve the consequences of this deficiency by administration of PGs have failed.

PGs have repeatedly been described as "ubiquitous" in mammalian tissues. Despite the fact that they occur in amounts usually under 1μg/gram of wet tissue, the identification in various mammalian species of PG-like substances in almost all organ systems has been reported. A number of independently discovered biologically active principles such as lung spasmogen, darmstoff, irin, and menstrual stimulant have been shown to owe their activity to PG-like substances. To date, human and sheep seminal plasma exceed all other tissues in their content of PGs, the total concentration in these instances exceeding 100μg/ml.

To the present, the PGs have eluded attempts at classifying them with other biologically active compounds. PGE_1 and PGE_2 are rapidly removed from the blood after intravenous injection during the first circulation through the vascular beds. It is not certain whether this is the result of metabolism or tissue uptake. The main metabolic sites are the lungs and the liver. Measurable levels of PGs in the circulation have only been reported in humans during labour and in patients with medullary carcinoma of the thyroid. In fact, of the clinically studied PGs, only PGA_1 and PGA_2 escape rapid inactivation in the pulmonary circulation and may theoretically function as circulating hormones by classical criteria. In being endogenous substances that can be liberated and quickly inactivated at many sites in the body, the PGs are not unlike the kinins and other "local hormones" or autocoids. Recent evidence suggests that at least part of their function might be the mediation of end-organ response to circulating hormones at the level of the cell membrane.

Over the last decade and a half, both fundamental and clinical investigations concerning the PGs have intensified phenomenally. Their extraordinary potency in some systems coupled with their apparent omnipresence in mammalian tissues were, and still are, interpreted as pointers towards perhaps several associated physiological roles. The result is a seemingly exponentially expanding pertinent literature which shows no signs of exhaustion. Dose-dependent and species variations of the activities of various individual PGs have often been reported as ranging between diametrical opposites.

In vivo experiments have been complicated by the multiplicity of their activities. Hypotheses abound but the preliminary nature of many of the investigations is compounding the problem of interpretation. Several good review articles have been written[1-4]. Because of the extensive nature of the subject at hand only a few aspects of it will be discussed here with special emphasis on recent unifying concepts and emerging possible clinical applications.

PGs AND THE RENAL-CARDIOVASCULAR SYSTEM

The first human pharmacological studies with a purified PG were reported by Bergstrom and colleagues who, on infusion of 0.2-0.7μg/kg/min of PGE_1 over 2-10 minutes, noted "tachycardia, reddening of the face, headache and an oppressive feeling in the chest" as well as a moderate fall in blood pressure. The vasodepressor effect of the PGs was one of their earliest actions to be recognized. It has subsequently been found to vary considerably depending on the individual prostaglandin involved. PGE_1 and PGE_2 are powerful and unequivocal vasodilators decreasing peripheral resistance and depressing systemic arterial blood pressure, an effect not blocked by alpha or beta adrenergic or cholinergic blockers or histamine or serotonin antagonists. They also reflexly invoke a hyperkinetic circulation characterized by tachycardia and decreased A/V O_2 difference.

$PGF_{2\alpha}$ activity on the cardiovascular system is subject to striking interspecies variation, being depressor in the cat and rabbit, pressor in the rat and dog and without demonstrable effect in man. It is likely that these discrepancies are only apparent and the observed effect is only the net result of the opposing effects on the blood pressure of the primary vasodilatation and the reflex sympathomimetic increase in cardiac index which may sometimes be of overcompensatory proportions.

The most interesting of the PGs with respect to renal and cardiovascular activities are the PGAs, distinguished from the others by their striking vasodepressor activity and lack of non-vascular smooth muscle stimulating activity. In 1965, a lipid acid named medullin was isolated from the rabbit renal medulla and was quickly identified as PGA_2. PGA_2 has been shown to be the most abundant PG in the renal medulla with PGE_2 also present in significant amounts. Moreover, because PGE_2 is converted to PGA_2 by nonenzymatic dehydration, it is difficult to ascertain the extent to which the latter is artifactual to the isolation procedure. In early studies using purified PGA_2 isolated from rabbit, Lee and his co-workers reported that in dogs and in a human patient with essential hypertension PGA_2 caused a short-term hypotensive action and marked diuresis.

Vasodepressor lipids have been isolated from human kidneys and concentrations of a PGE_2-like lipid of 40-234 ng-equivalent/ml were detected in the renal venous blood of hypertensive patients but none in normotensive subjects. Recent evidence is available suggesting that the PG-induced electrolyte and water losses stimulate the renin-angiotensin system, possibly by way of chemoreceptors in the area of the macula densa cells in the distal

tubule. PGA compounds are certainly among the most potent natriuretic agents known in that they are effective at concentrations of 1ng/ml of renal arterial blood. When administered to man at low infusion rates of 0.1-0.3μg/kg/min. rates which do not affect arterial blood pressure, urine flow and free water clearance rise significantly. At higher infusion rates the effects are reversed with renal plasma flow, urine flow and electrolyte excretion falling to control values.

Recently, McGiff and co-workers have shown that angiotensin II induced the release of PG-like substances in dogs and suggested that an alteration of the balance between pressor substances (renin, $PGF_{2\alpha}$) and depressor substances (PGE_2, PGA_2) may determine the development of renal hypertension. In the light of more recent evidence to be described later concerning the possible role of PG receptor-sites in the ovary and thyroid it is not unlikely that aldosterone release from the adrenal cortex under the influence of angiotensin II may be similarly mediated.

The potent vasodepressor and natriuretic activities of the PGAs made them attractive candidates for clinical evaluation in the renal-cardiovascular field. Current clinical studies are being carried out using PGA_1 mainly because of its more ready availability and biological activity apparently equivalent to that of PGA_2. Most of these studies are of a preliminary nature and indicate a reduction in blood pressure during infusion of PGA_1 accompanied by an increase in the renal fraction of the cardiac output, enhancement of free water clearance and sodium diuresis.

The exact mechanisms of the action of PGs on the vascular smooth muscle or on the kidney are not yet understood. However, there is much recent evidence that many of their actions at the cellular level are related to the modulation of cyclic-AMP (cAMP) perhaps through an effect on the adenyl cyclase enzyme system to be discussed later in this article. Besides peripheral arteriolar relaxation, PGA_2 has been demonstrated to cause a redistribution of flow from the outer medulla to the cortex of the kidney associated with an absolute increase in renal cortical blood flow. This effect has also been observed with ethacrynic acid, furosemide, acetylcholine and saline. It is not likely that the natriuresis produced by PGA or PGE compounds is the result of the inhibition of the cortical metabolic energy sources necessary for sodium transport. The most likely explanation for natriuresis accompanying the increased renal plasma flow is thought at the present to be diminished proximal tubular sodium reabsorption secondary to an increase in peritubular hydrostatic pressure with an increased delivery of sodium to more distal sites. This, in turn, could lead to the observed increase in distal tubular sodium transport leading to the observed increase in free water clearance accompanying the PGA_1-induced natriuresis.[5]

There is much evidence supporting an endocrine antihypertensive role of the normal kidney in the regulation of vascular tone. The exact relationship of the renal PGs to this function, however, is not clear. Much more work will be required before the role of PGs in the physiological regulation of blood pressure or their place in the treatment of pathological conditions are elucidated.

PGs AND THE REPRODUCTIVE SYSTEM

The PGs have to date been implicated in numerous aspects of the functions of the reproductive organs.[6]

In 1963 the menstrual stimulants responsible for the powerful and coordinated uterine contractions causing the extrusion of sloughed endometrium were identified as PGE_2 and $PGF_{2\alpha}$.

The effects of PGs on the myometrium and oviducts have been extensively studied. *In vitro,* PGEs inhibit while PGFs stimulate the activity in the non-pregnant human myometrium, its sensitivity varying considerably with the hormonal state, being maximal to the former during ovulation and the latter prior to menstruation. PGEs relax the cornual segment and contract the remainder of the human fallopian tube. *In vivo,* the deposition of seminal fluid extract in the vagina results in inhibition of uterine contractions only if administered simultaneously with intravenous posterior pituitary hormones. Presumably such inhibition might facilitate the ascent of sperm to the site of fertilization.

Knowing that the concentration of PGs in human seminal plasma is the highest found in any tissue tested to date, it is hardly surprising that one of their first functions sought was related to fertility. It was not until 1969, however, that the results of a study on 137 different semen samples obtained from men with documented normal fertility, from men in infertile marriages of unexamined origin and from men in "functionally" infertile marriages indicated with statistical significance that the concentration of PGEs in human seminal fluid is of importance for normal fertility. In fact, 40% of the husbands of infertile couples were shown to have a relative deficiency of PGEs in their semen.

Whether the seminal PGs act on the female reproductive tract locally or systemically, if at all, is not established. Using tritiated PGs, their absorption from the human vagina in amounts sufficient to affect tubal motility has been established. The deposition of bacteria-free sperm suspensions into the uterine lumen of the rabbit results in the invasion of the lumen by polymorphonuclear leukocytes. The presence of leukocytes in the female reproductive tract is essential for capacitation of spermatozoa to occur. As PGE_1 has been shown to possess leukotactic properties, it may play a role in the process of sperm capacitation.

In spite of large interspecies variation of seminal fluid PG concentrations ranging from undetectable to very high, PGs may play a role in the control of the functions of accessory genital organs in the male such as seminal

vesicle emptying. In some species, the vas deferens is reactive to concentrations as small as 10^{-10}M. Potentiation of adrenergic and inhibition of neural stimuli have also been demonstrated in these organs.

The physiological role of PGs in human fertility is far from defined. In other mammalian species the observations seem even more equivocal and the low PG content in the seminal fluid of many of them, in the face of excellent reproductive capacity, does much to discourage unfounded speculations in this area, in particular as far as effects involving the female reproductive tract are concerned.

By contrast, the role of PGs in relation to parturition is better documented. *In vitro* studies show that while the lower segment myometrium in pregnancy is relatively unresponsive, the upper segment is markedly stimulated by both PGEs and PGFs. PGE_1 has a complex effect on the motility of the pregnant human myometrium *in vivo*, being inhibitory at high doses (0.3μg/ml) but stimulatory at smaller doses (0.01μg/ml).

Amniotic fluid was found to contain high levels of PGs only in patients in spontaneous labour. PGE_2 and $PGF_{2\alpha}$ are present in the maternal circulation with progression of labour, $PGF_{2\alpha}$ appearing in increasing concentrations. A striking correlation between $PGF_{2\alpha}$ concentration and the labour contractions was noted, rising immediately prior to, highest during, falling sharply after and being undetectable between contractions.

Parenteral, oral and intravaginal PGE_1 and $PGF_{2\alpha}$ have been used with success in the induction of labour at or near term[6, 7]. The degree of success reported varies with the investigator and presently large scale well controlled studies are being conducted to compare their efficiency with that of the presently used oxytocic agents. Compared to oxytocin which acts quickly, the PGs are slow in action, their effects persisting after infusion is stopped, but well controllable by the rate of infusion. The pattern of uterine activity induced by PGE_2 and $PGF_{2\alpha}$ infusion is similar to that of spontaneous labour. Optimism coupled with caution surrounds their possible future clinical use.

The above observations seem to support, though they by no means should be construed as proof of, a physiological role of PGs in human parturition[7].

During spontaneous abortion at 10-24 weeks, amniotic fluid contains high levels of PGE_2 and $PGF_{2\alpha}$. Intramuscular, subcutaneous and intravaginal PGs during the first and second trimester of pregnancy stimulate the uterus and have been used for therapeutic termination of pregnancy[7]. By contrast to oxytocin, the myometrium in early pregnancy is quite reactive to PGs, the reported extent of this effect varying from investigator to investigator. On this basis, the PGs may become clinically useful in the future as abortifacient agents.

Under conditions where conception and uterine implantation do not take place, the corpus luteum of many mammalian species regresses under the influence of the ipsilateral uterine cornua. The resulting fall in levels of circulating progesterone is followed by endometrial degeneration and menstruation. The development of the corpus luteum is known to be under the control of pituitary hormones but the mechansim of its regression is unknown. $PGF_{2\alpha}$ is luteolytic when administered either by continuous infusion or parenteral injection to a variety of mammalian species. It has been reported to be released from the guinea pig uterus under conditions which stimulate luteolysis and to reduce venous outflow from the utero-ovarian vein and one of the postulated mechanisms of its action is by inducement of ovarian ischemia. This view fulfills the criterion of ipsilateral cornual influence characterizing the physiological luteolysin. However, neither the identity nor the mechanism of action of luteolysin are settled at the present. As will be noted later, $PGF_{2\alpha}$ has been found to enhance progesterone production by the ovary *in vitro*, a finding that apparently contradicts those of others *in vivo*. Furthermore, the ovarian ischemia theory is also under heavy fire. An intriguing speculation is that luteolysins are transported directly from the utero-ovarian vein to the adjoining highly adherent uterine artery which takes a tortuous course on its surface. This would be a very ingenious way of getting the possibly highly labile PGs from the uterus to the ovary without passing through the lungs which have been shown to quickly remove them from the circulation. Even if this were the case, the question of whether the luteolysis thus invoked is mediated by gonadotrophin antagonism, by a decrease of ovarian blood flow, by a direct effect on the ovary, or by some other means would remain unsettled.

Administered at appropriate times after mating, $PGF_{2\alpha}$ prevented or reduced the incidence of pregnancy in rats, rabbits and monkeys. This effect is likely due to luteolysis since it can be reversed by progestin replacement and falling levels of circulating progesterone preceded any signs of termination of pregnancy.

Infusion of $PGF_{2\alpha}$ in non-pregnant women induced vigorous uterine contractions and menstrual-like bleeding in the secretory phase of the cycle. Thus the time interval immediately following the first missed menstrual period may be optimal for the prevention of blastocyst implantation by PG administration. Timing is essential for this to occur and may well prove to be the hardest problem in this possible clinical application[8].

PGs AND cAMP

PGE_1 is one of the most potent inhibitors of lipolysis known. Using glycerol and free fatty acid (FFA) release as indicators of lipolysis, PGE_1 at concentrations as low as 1ng/ml significantly inhibited both basal and sympathetic nerve stimulated lipolysis in the epididymal fat pad of fed rats. Similar effects have been demonstrated using

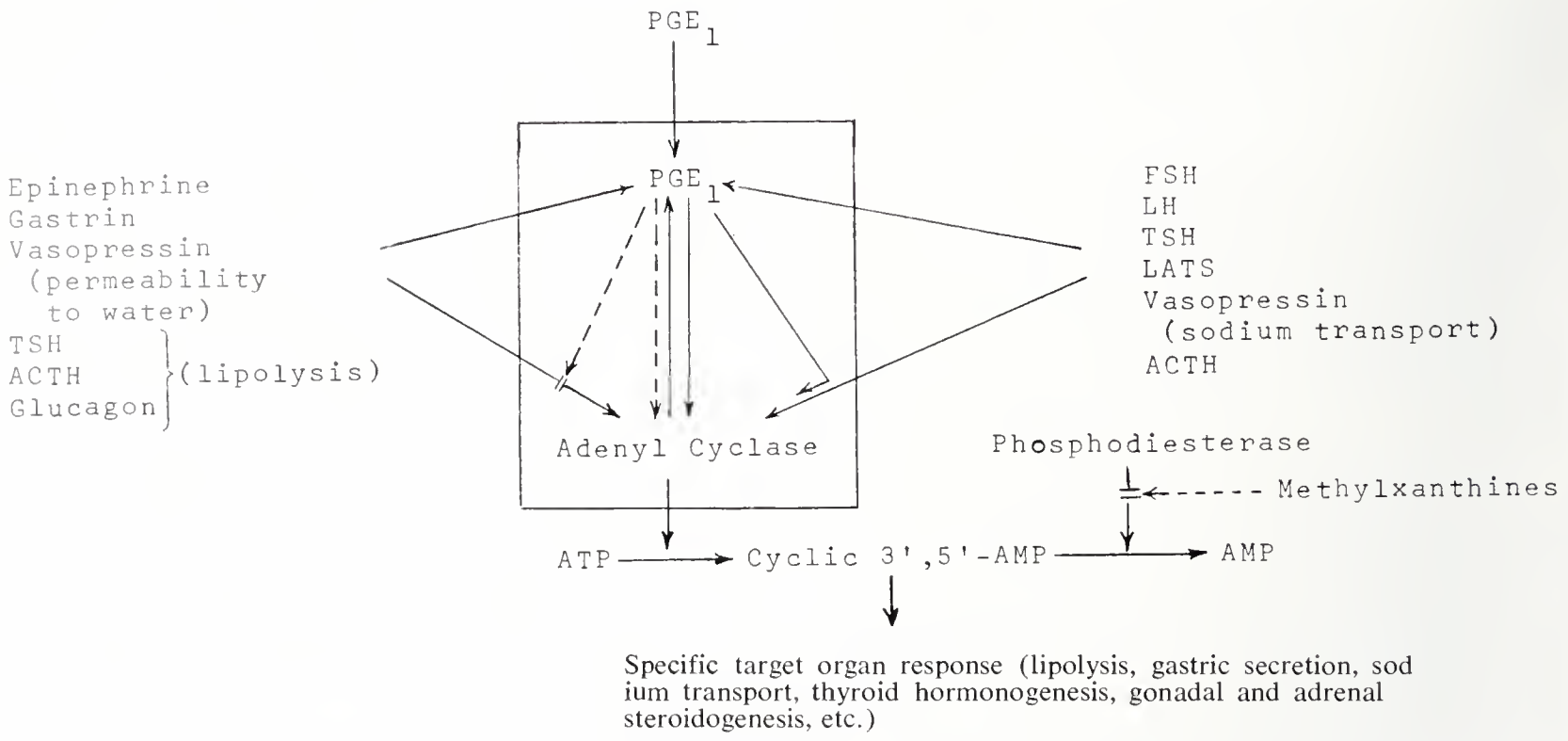


Fig. 2 Schematic diagram of some possible mechanisms of action of PGE_1. Elements within the square box are associated with cell membrane.

human adipose tissue *in vitro* and isolated white fat cells (human and rat).

In vivo studies have been complicated by the fact that at small infusion rates PGE_1 seems to stimulate FFA mobilization. However, this effect can be abolished by ganglion blocking agents and mimicked by a variety of unrelated hypotensive agents indicating that the observed effect is probably due to the reflex compensation by the sympathetic system to the hypotensive effect of PGE_1.

Lipolysis induced by catecholamines, glucagon, corticotrophin (ACTH), thyroid stimulating hormone (TSH), arginine vasopressin and others is inhibited by low concentrations of PGE_1. As with basal lipolysis, PGE_1 is a potent inhibitor: in the fat pad, 3.2ng/ml significantly inhibits the effect of 100ng/ml of epinephrine with maximal effect occurring at 100ng/ml (41% inhibition). In isolated white fat cells, PGE_1 completely blocks the effect of an equal amount of epinephrine.

The hormone-sensitive lipase determining the rate of lipolysis induced by the above mentioned hormones is known to be mediated by the activation of the adenyl cyclase enzyme system and increased conversion of adenosine triphosphate to cyclic 3^1, 5^1-adenosine monophosphate (cAMP), Sutherland's "second messenger" (See the article by H. Strauss in this issue). Thus it seemed reasonable to further investigate the activity of PGE_1 in relation to its ability to influence the cAMP mechanism especially since it has also been shown to block the vasopressin-induced increase in water permeability of the isolated toad bladder and rabbit renal tubule, actions known to be mediated by the same mechanism.

Investigations along these lines revealed that in the epinephrine stimulated fat pad the increase in lipolysis was preceded by and correlated well with rising levels of cAMP and low concentrations of PGE^1 antagonized both effects. However, PGE_1 failed to antagonize the lipolytic action of dibutyryl cAMP (a derivative of cAMP that mimics its actions but penetrates the cells more readily). The conclusion was that PGE_1 acts by inhibiting the adenyl cyclase enzyme system rather than by accelerating cAMP destruction by stimulating phosphodiesterase (Fig. 2). Theophylline stimulates lipolysis probably by inhibiting phosphodiesterase. PGE_1 inhibits theophylline-induced lipolysis in rat adipose tissue. Exactly how this action is mediated is not yet understood.

Gastric secretion in response to a variety of secretagogues is believed to be mediated at least in some species via cAMP formation and it could be expected that PGE_1 would inhibit gastric secretion by blocking adenyl cyclase in the gastric parietal cells. PGs are released into the rat stomach spontaneously and in response to various stimuli. Intravenous infusion of PGE_1 at rates of 0.5-1.0μg/kg/min markedly inhibited gastric acid secretion in dogs stimulated by food, histamine, pentagastrin, or 2-deoxy glucose. PGE_1 and PGA_1 were also found to be active while $PGF_{2\alpha}$ had no effect. It has been shown that this decrease was probably not the result of restriction of gastric mucosal blood flow but rather a primary mechanism. In man similar results were obtained when PGE_1 was administered intravenously but not when given orally.

However, these results are too preliminary to establish any conclusion as to a possible clinical utility of PGs in the treatment of peptic ulcer.

As mentioned earlier, PGE_1 inhibits the water-permeability response of the toad bladder to vasopressin but not to cAMP. Available evidence seems to indicate that this effect is mediated by inhibition of the vasopressin enhancement of the adenyl cyclase enzyme perhaps by decreasing the affinity of the vasopressin-receptor site interaction. At the same time recent evidence[9] suggests that PGE_1 stimulates the cyclase system responsible for active sodium transport in the toad bladder, the cAMP pool generated in this fashion being independent of the one determining water permeability. This may well explain why PGE_1 actually increases the amount of cAMP in this tissue. Thus it appears that PGE_1 has two opposite actions on adenyl cyclase in the apparently independently operating water and sodium transport systems in this preparation.

By 1967 evidence had accumulated that PGs, under at least one experimental condition, antagonized every one of the hormones whose actions on their specific target tissues were known to be mediated by way of the adenyl cyclase system. This, coupled with the observation that in many instances they were concomittantly released from various target tissues prompted the speculation that PGs may act as general modulators of the cyclase system perhaps providing a negative feedback loop in the intracellular component of the effect of circulating hormones. Already at that time there were indications of more complexities to follow. PGE_1 when acting alone, increased cAMP levels in whole fat pads without activating lipolysis. The site of this paradox did not appear to be the fat cell itself which, when isolated, didn't exhibit this effect. In many tissues such as lung, spleen, brown fat, diaphragm, testis, brain and kidney, PGE_1 increases cAMP concentration. A most marked increase occurs in platelets, this being further potentiated by theophylline.

The activity of adenyl cyclase in lysates of human platelets is responsive to PGE_1 at concentrations of 2ng/ml. The functions of the human platelets which are mediated through cAMP have not yet been determined. However, ADP-induced aggregation of human platelets *in vitro* can be inhibited by concentration of PGE_1 as low as 10^{-8}M with maximal effect at about $3X10^{-7}$M. The dose-response curve is quite similar to that seen for the activation of adenyl cyclase by PGE_1 suggesting that cAMP is important in platelet aggregation. Platelet aggregation by a variety of other agents including thrombin has also been shown to be inhibited by PGE_1. PGE_2 is approximately 30% as effective as PGE_1 in this respect.

The PGs have been shown to serve possibly as negative feedback mediators of the cAMP system only in the action of lipolytic hormones on adipose tissue, of vasopressin on the kidney tubule and of gastrin on the rat stomach mucosa. In all other tissues studied, PGE_1 was found to stimulate the function of cAMP and thus mimick the actions of the circulating hormones in question. This effect has been shown to hold for the action of ACTH on the adrenal, of FSH on the testis, of LH on the ovary and of TSH and LATS on the thyroid.

The recent development of PG antagonists was perhaps one of the most important milestones in the course of investigative efforts in the field. 7-oxa-13-prostynoic acid is structurally a PG analogue and is the result of systematic chemical synthesis. Polyphloretin phosphate (PPP) is a polymeric phosphorylated polyionic derivative of phloridzin that was known to potently inhibit alkaline phosphatase, hyaluronidase and urease as well as diminish the formation of serous exudates. About a decade ago, it was observed to antagonize the rise in intraocular pressure in the rabbit produced by ocular irritation. The irins which were implicated in this phenomenon have since been identified as PGs and PPP was found to abolish the rabbit eye response to intracameral injections of PGE_2. Both these antagonists have been shown to be selective in a variety of preparations, their inhibitory actions behaving in competitive fashion with respect to the PGs.

Based on a dose-response relation between PGs and the formation of cAMP in the mouse ovary 7-oxa-13-prostynoic acid was found to competitively block the stimulatory effect of PGE_1, PGE_2 and LH on cAMP. Rigorous kinetic studies indicate that there is a single LH-related PG receptor site in mouse ovaries, its activation being essential in the action of LH stimulation of cAMP and steroidogenesis[10].

Similar recent studies on isolated bovine thyroid cells seem to indicate the presence of a PG receptor site the activation of which may be an early step in the action of both TSH and LATS on thyroid.[11]

Membrane receptor sites have for long been a cryptic entity. In fact, so little is known about their nature that they have been handled as concepts rather than biomolecular realities. The PGs known to be associated with the cell membrane may well provide an opportunity towards the development of our understanding of membrane receptors.

In his beta adrenergic theory of the atopic abnormality in bronchial asthma, Szentivanyi[12] has defended the possibility that the fundamental abnormality of atopy may be a deficiency in adenyl cyclase. In his thesis he demonstrates that beta adrenergic failure at the target organ level could account for most of the characteristics of bronchial asthma and points out that the same considerations may well apply to the manifestations of atopic allergy affecting nasal mucosa, skin or gastrointestinal tract. In connection with this view, the ability of the PGEs to modulate adenyl cyclase is of great significance especially since the site of this effect, though not exactly identified, appears to be past the initial beta adrenergic receptor site.

Bronchoconstriction caused by histamine, serotonin, acetylcholine or bradykinin has been shown to be prevented by intravenous PGE_2 in anaesthetized guinea pigs. Bilateral vagotomy, adrenalectomy, double pithing or pretreatment with reserpine or pronethalol did not abolish this effect. Administered as an aerosol, PGE_2 prevented bronchoconstriction in normal and in horse serum-sensitized guinea pigs being as active as isoprenaline but of shorter duration of action. Preliminary experiments in healthy and asthmatic volunteers on the effects of PGE_1 and isoprenaline on the timed forced expiratory volume in one second (FEV_1) showed that if the neutral non-irritating triethanolamine salt of PGE_1 was used as an aerosol it could cause substantial reduction in airways obstruction in asthmatic patients.

In dogs, PGEs were equipotent (about 5μg/kg) to epinephrine but their duration of action was more than seven times as long in reducing resistance offered by the nasal passage to a constant stream of humidified air when injected into a carotid artery. Preliminary studies in human volunteers receiving PGE_1 topically via an atomizer showed encouraging results in this respect. Doses of 37-100 μg. applied to one nostril caused an increase in the patency of the nasal airway and visible blanching of the nasal mucosa.

These observations could well be due to facilitation of cAMP production and rectification of the atopic deficiency outlined by Szentivanyi.

OTHER EFFECTS OF PROSTAGLANDINS

One of the earliest observed effects of PGs were those on the smooth muscle of the gut wall. PGs have been shown to occur naturally in the gut wall and *in vitro* studies have demonstrated the ability of PGEs to inhibit and of PGFs to stimulate peristaltic activity. In man, intravenous infusion of PGE_1 causes abdominal cramps while oral administration of 0.8-3.2mg results, after a delay of several hours, in loose watery stools presumably due to increased intestinal propulsion. Infusion of PGE_1, PGA and $PGF_{2\alpha}$ into the superior mesenteric arteries of dogs, with isolated loops of small intestine, produces a net loss of fluid from these segments. $PGF_{2\alpha}$ produces this effect when infused at less than 1.0μg/min. The same phenomenon is reproducible with theophylline, which as cAMP and cholera enterotoxin has also been shown to produce an inhibition of net sodium absorption and elicit net chloride secretion. PGE_1 and $PGF_{2\alpha}$ inhibit sodium absorbtion, the former being active at 1.0 nanomolar concentrations when applied to the serosal side. This effect is quite possibly due to stimulation of adenyl cyclase and rising gut cAMP levels. Thus this mechanism could also account for the diarrhea observed. While the physiological role the PGs might fulfill in gastrointestinal motility is unknown, a pathological role for circulating PGs seems possible since they are sometimes released into the bloodstream from certain tumours in patients who have associated diarrhea.

The mechanism of the vasodilatation accompanying stepped-up activity in many organs (functional hyperaemia) has been an unsolved mystery for a long time. In exocrine glands this phenomenon has been shown to be due likely to the release of kinins. In skeletal muscle the mechanism remains unexplained. The importance of sympathetic vasodilator fibres supplying the vascular beds of skeletal muscle as well as the role of the generally accepted possible mediators such as O_2 lack, lactic acid accumulation and pH changes have been shown to be only of minor importance. During the prolonged functional vasodilatation of adipose tissue, the appearance of vasodilator substances resembling PGs has been demonstrated. PGEs have been shown to mimick the actions of these substances when exogenously injected into the fat pad circulation. ACTH is known to increase adrenal blood flow, an effect apparently independent from that on steroidogenesis. A role similar to that in adipose tissue has been ascribed to the PGs with respect to functional vasodilatation in endocrine glands.

It is impossible to even enumerate here all the physiological and pathological processes in which the PGs have been implicated. Some of the more important ones that had to be left unmentioned are their actions on the nervous system, effects on carbohydrate metabolism and their role in inflammation and anaphylaxis.

Perhaps this might be a good time to return to a discussion of the mechanism by which PGs might affect smooth muscle. Before discussing their direct smooth muscle actions, it should be pointed out that recent evidence indicates that the PGs interact with the sympathetic neuroeffector system at the presynaptic as well as postsynaptic level of the nerve-muscle interface. Their striking effects on neural tissue possibly by a modulation of central interneuronal adrenergic transmitter functions have not been discussed here but good accounts of these may be found in the review articles[1-4]. Although a presynaptic sympathetic component has been demonstrated in various tissues, most of their activities have been found to be at least partly and often wholly non-neural.

The character of the PG - cAMP relationship may be expected to determine the extent to which the PGs mimick beta adrenergic effects at various sites. The beta adrenergic-like effects of bronchial relaxation, vasodilatation and ocular miosis may be interpreted as reflecting an agonistic PG - cAMP relationship such as that in the thyroid cell. Unfortunately no information is as yet available on this relationship in the tissues mentioned and the PGs may act independently of cAMP mediation.

There is strong evidence indicating that relaxation of uterine smooth muscle to catecholamines is in fact mediated by the cAMP system. Oxytocin stimulates the uterus without altering the level of cAMP and is a potent antagonist of the relaxing effect of the dibutyryl derivative of cAMP. As well, the PGs that normally contract certain uterine muscle preparations are markedly

inhibited in this effect by cAMP in a manner not unlike oxytocin. Thus it seems that in this instance the PGe may cause a fall in levels of cAMP as they do in the fat cell.

The exact biochemical-mechanical coupling in smooth muscles is poorly understood. Whether acting by way of cAMP or not, PGE_1 has been shown to increase calcium ion flux in certain cardiac muscle preparations. However any statement about the effect of PGs on calcium binding or transport would be mere speculation.

The apparently dualistic effect of the PGs on cAMP in various tissues is intriguing. If indeed they are membrane-bound modulators of the adenyl cyclase system, they appear to possess a potentially bidirectional action the ultimate direction of which depending on the cell type or perhaps on the subcellular compartment they subserve. The PGs may thus provide an intermediate step in the information transfer from the extracellular to the intracellular compartment, the degrees of freedom of its responses being less than that of the gamut of receptor sites on various cell membranes but more than the unidirectional universal response of cAMP levels to stimulation of the adenyl cyclase enzyme system. Thus, as well as fulfilling the role of information transduction they appear eminently endowed to act as mediators of intracellular feedback loops and as branching points for compartmentalized subcellular functions. Examples of each of these have been described in this presentation.

CONCLUSION

Discovered over 40 years ago, the ubiquitous PGs are being assigned an ever increasing number of physiological and pathological functions. Their generalized relationship to the "second messenger" system has rendered them plausibly of universal significance. The discovery of PG antagonists and the more recent development of a radioimmunoassay will no doubt improve the resolution of investigations and lead to many rapid advancements in the field. The PGs hold great promise in contributing both to our clinical therapeutic armamentarium as well as to our understanding of biological phenomena at all levels of organization from the organism as a whole to the biomolecular intricacies of subcellular processes.

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Froehlich's Syndrome Revisited

A. F. Jahn, 7T4

Thirty-five hundred years ago in the New Kingdom of Egypt, the young pharaoh Amenophis IV ascended the throne of Egypt. Under his assumed name of Akhenaten the new king radicalized the thousand-year-old religious beliefs of his country, introduced monotheism centering around the sun-god Aten, saw the kingdom attain new heights of power and became, in the words of Cyril Aldred, the first *individual* in human history.[1] He took as his chief wife Nefertiti, a woman of possibly Asiatic origin, who bore him six daughters. In the later years of his reign the queen lost favour and Akhenaten took as co-regent his brother Smenkhare, a boy in his late teens.

Smenkhare and Akhenaten carried on a homosexual relationship. The boy died in 1363 BC in his early twenties, and Akhenaten, after 16 years of reign, died the following year. The worship of the one god Aten was buried with him as the priests of Amun reclaimed power. The heretic was succeeded by his 9-year-old brother, the pharaoh Tut-ankhamen, a child who in modern times attracted undue attention.

Among Akhenaten's many reforms was a new trend towards realism in art, the so-called Amarna period of humanism[2] that departed radically from the stylized depictions of pre-Akhenaten 18th dynasty Egypt. In times following the very name of Akhenaten became anathema and two subsequent dynasties attempted, unsuccessfully, over the next 300 years to erase all traces of the heretic king. Fortunately numerous depictions of Akhenaten remain and the pharaoh's peculiar physiognomy is a perennial puzzle to Egyptologists and physicians.

In 1901 the Viennese neurologist Alfred Froehlich described a case of hypogonadism asociated with an absence of secondary sex characteristics, and marked adiposity in a 14-year-old boy. He demonstraetd the cause of the disease to be a cranio-pharyngioma and treated the patient surgically, with subsequent alleviation of the symptoms.[3] Hypogonadism and adiposity demonstrated in conjunction with a pituitary tumour around the age of puberty have since borne the name of Froehlich's Syndrome, to the great chagrin of Babinski who described an identical case one year earlier.

The appearance of Akhenaten was indeed strange. An excavation by Petrie in 1891 at Amarna shows him in profile with marked prognathism, large lips and coarse features, notable gynecomastia and generally female fat distribution with pronounced buttocks and hips and thin extremities distally. The colossus uncovered at Karnak by the Egyptian Antiquties Service in their excavations between 1926-32 represents the pharaoh possessing the above features along with a pendulous full abdomen and notable absence of genitals. Most Egyptologists dismissed these findings with the suggestion that Akhenaten was a woman masquerading as a man. After all, Queen Hatshepsut a hundred years earlier assumed the role of pharaoh in full male regalia complete with false beard. John Pendlebury[1] however considered the findings "a wonderful pathological study". He thus initiated an inquiry which has reached a plateau recently with the consideration that Akhenaten suffered from classical Froehlich's syndrome.

Unravelling the threads of the story was no easy matter. In 1907 Davis uncovered a tomb in the Valley of the Kings (which was labelled Tomb No. 55) containing the putative remains of the Heretic. The pelvis in the grave was diagnosed, by an American obstetrician, as female. Later examination showed that the pelvis had a subpubic angle of merely 67°, proving the remains to be male. Gross examination of the skull suggested some distortion of vault architecture. Scientists who proposed that the skull was Akhenaten's quickly pointed out that some degree of hydrocephalous is often found with Froehlich's dystrophy. They further demonstrated an erosion of the sella turcica, a finding compatible with a pituitary tumour.

The monumental task of detailed anatomical examination and reconstruction of the skeleton was undertaken in 1966 by Dr. R. G. Harrison, an anatomist. His findings[4] suggest that the skeleton was that of a 22-23-year-old youth, not Akhenaten. His calculations were based primarily on the degree of epiphysial closure. It was suggested that delayed closure of epiphyses can be expected in endocrinopathies, with a thirty-five year old demonstrating the epiphysial age of a twenty year old. Harrison however affirmed that the skull vault was not distorted by hydrocephalus, merely wide in the biparietal diameter, a genetically transferred essentially normal variant.

The sutures also were intact, not splayed open as may be expected in late onset hydrocephalus. The sella erosion was shown radiologically to be a post-mortem artifact. Finally, reconstruction of the face displayed features similar to those of Tut-ankhamen. Since Smenkhare and Tut-ankhamen were known full brothers, the remains are now accepted as those of the young co-regent.

Cyril Aldred and A. T. Sandison[5] after much armchair rumination arrived at the conclusion that Akhenaten suffered from adiposo-genital dystrophy of the Froehlich's type. Their final diagnosis of pituitary hyperfunction followed by hypofunction and secondary hypogonadism is reconcilable with a craniopharyngeal cyst encroaching upon the adenophypophysis, gradually compromising its function. Their conclusion leaves two open ends. Their study took place before Harrison's work and hinged on the assumption that the excavated skeleton was Akhenaten. They further found difficulty in reconciling the pharaoh's documented fatherhood with the obvious sterility and impotence of Froehlich's syndrome.

Did Akhenaten have true Froehlich's syndrome? I feel that there are several factors to be considered which

circumstantially suggest endocrinopathy from a late onset, post-pubertal tumour.

Of prime consideration is the obvious prognathism and acromegalic facies. These are suggestive of a post-pubertal hypersecretion of growth hormone. There is no evidence of gigantism, somatotropin hyperfunction prior to epiphysial closure. Froehlich entitled his original article "Ein Fall von Tumor der Hypophysis cerebri *ohne Akromegalie*" the title similar (verbatim) to Babinski's paper. Thus Froehlich's syndrome by definition excludes acromegaly. Akhenaten lived a shortened life span which may have been curtailed by an early onset tumour. A small percentage of craniopharyngiomas will turn malignant and invade the brain and an early onset tumour could possibly cause significant damage.

We must further consider Akhenaten's six daughters, one of whom later became Tut-ankhamen's queen. Aldred suggests that these girls were fathered by another man,[5] and rallies as evidence the fact that the pharaoh was unable to sire a male heir.[1] This chain of reasoning is not logical. Much more likely the pharaoh reached puberty, procreated and then suffered the effects of hypogonadal disorder. Reports have been recorded[8] of chromophobe adenomas which produced a gonadal involution and reduction in the size of the external genitalia after normal puberty.

Akhenaten's early representations show him an uxorious man, always in the company of his wife and daughters. Only in later life did he choose a new mate, the youth Smenkhare. A limestone stela from Amarna shows the two kings seated, Akhenaten embracing Smenkhare, obviously the active party in the homosexual relationship.

A post-pubertal loss of masculine gonadal function would account for the pharaoh's early heterosexual relationship with *Nefertiti* and his subsequent homosexual ties. A further consideration hinges on the art styles of Akhenaten's times, which divides nicely into three periods. The first period of classicism shows the pharaoh with no disability in the stylized attitude of his forebears. A full length seated statue of the pharaoh with his mother Queen Tiye exhibits no acromegaly and minimal gynecomastia as can normally be expected at prepuberty. The second period, Amarna humanism, depicts the king realistically with all the ravages of his affliction. The third period of idealised realism presents the unmistakably pathological features of the king but minimises the signs of his disease. A yellow steatite statue acquired by Henry Salt in 1826 at Thebes illustrates this period well.[2] Is it coincidental that this sequence of "styles" corresponds to the progress of a possible post-pubertal adiposogenital dystrophy?

Another loose end is a sketch of Akhenaten, found at Amarna, which shows a profile sparsely covered with beard of a few days' growth, apparently unshaven in mourning. Facial hair is a secondary male sex characteristic dependent directly on testosterone secretion, thus the diagnosis of Froehlich's again comes into question. Aldred suggests that the beard may be false, donned for the occasion, yet this is no typical pharaonic false beard but a real 5 o'clock shadow.

In 1936 Dr. Bela Mittelmann[6] published a psychiatric study of juvenile adiposo-genital dystrophy. He qualifies his cases as non-neoplastic in origin but his findings are still of interest here. He found a poverty of drive related to low metabolic rate, with passive, submissive, overdependent behaviour developing into either withdrawal or hostility. These qualities are difficult to attribute to the heretic king whose monumental career changed the world.

So I feel that the question of Akhenaten's pathology and its consequences is still wide open. Immanuel Velikovsky, a self-proclaimed gadfly to social scientists everywhere, has even published a study suggesting that Akhenaten is the real historical model for Oedipus Rex. Is the dilemma merely a question of wording? Possibly, since only in recent years has the clinical entity of pseudo-Froehlich's syndrome[7] has been described.

In 1948 Simpson postulated a male endocrine disorder which he calls adipose gynandrism[5]. Akhenaten may have suffered from this ailment. Before this discussion submerges in the semantic quagmire of pseudopseudohypoparathyroidism, I will terminate.

The archeological findings on Akhenaten may fit many theories. It was noted at the post-mortem examination of Napoleon Bonaparte that the emperor possessed grossly underdeveloped genitalia burried in many inches of pubic fat arranged in an unmistakably feminine distribution.[6] Did Napoleon have Frochlich's syndrome? But that is another story.

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Subacute Thyroiaitis

John McCormick, 7T2

CASE HISTORY

In mid-March 1970, Mrs. B. M., age 41 years, developed a mild respiratory infection featuring a sore throat, lack of energy, nausea and loss of appetite, clearing in several days. Two weeks later the patient developed laryngitis associated with redness of the pharynx. This discomfort cleared in 2 days but was promptly replaced by a pain of a different nature located in the thyroid region, radiating to the neck. Her temperature rose to 100 degrees F. This distress lasted for about 2 weeks during which time she felt otherwise well. In mid-April symptoms suggestive of hyperthyroidism developed, i.e., weakness, fatigue tremor, nervousness, rapid heart beat, exertional dyspnea, heat intolerance, excessive sweating, decrease in appetite and some generalized muscle soreness. Over the next 2 weeks the patient lost 11 pounds.

On May 5, 1970, physical examination revealed a pleasant, slender, relaxed woman. There was a slight rapid tremor of the extended fingers, and the skin felt normal. The thyroid gland was firm, smooth, extremely tender and diffusely enlarged with the right lobe slightly larger than the left. Its estimated weight was 35 to 40 grams. It moved with swallowing. There was no bruit over either lobe. There was no associated lymphadenopathy. Her chest was clear and the heart rate was 96 with regular rhythm. Blood pressure 124/80. There was no cardiomegaly and the heart sounds were of normal intensity. A soft apical systolic blowing murmur was audible. The remainder of the physical examination was within normal limits.

LABORATORY INVESTIGATIONS

Hemoglobin 12 grams%; white blood count normal; smear and differential normal; sedimentation rate (ESR) 62mm./hour; urinalysis normal; random blood sugar 97mg.%; serum thyroxine (T4) 19.4ugs.% (normal 4.5 - 11.5); triiodothyronine (T3) resin uptake 37.3% (normal 24-34%); radioiodine uptake 2% (normal 12-40%); tanned red cell agglutination titre (TRCA test) negative; chest x-ray normal.

COURSE AND MANAGEMENT

The diagnosis of subacute thyroiditis was made. The treatment recommended was rest and acetylsalicylic acid. Steroids were withheld.

On May 19, 1970, the patient returned to the office still suffering fatigue but noting a distinct decrease in the tenderness in her neck. Heat intolerance was less marked and her weight had stabilized at 96 pounds. The tremor was less noticeable than before. On examination this time, her heart rate was 92. The thyroid gland was slightly firm diffusely and was minimally tender. Its estimated weight was 25 grams. The ESR was 25 mm./hour; the T4 13.9ugs.%; and the T3 resin uptake 36.9%. Again it was suggested that the patient rest as much as possible and that acetylsalicylic acid be used for pain relief.

On September 15, 1970, the patient returned for a follow-up visit feeling well. She had no neck soreness and was judged clinically to be euthyroid. The ESR was 18mm./hour. All thyroid indices were within normal limits. The TRCA test and the Complement Fixation (CF) test were negative. The patient has since suffered no recurrences.

Subacute thyroiditis (SAT) is an inflammatory disease of the thyroid gland of probable viral etiology. It is usually self-limiting and lasts from one week to over a year, but generally 3 to 4 months. Clinically it presents with widely ranging enlargement of the gland with variable manifestations from no systemic symptoms to very severe thyroid pain and tenderness, dysphagia and systemic signs of malaise, fever and/or severe hyperthyroidism. Although Subacute Thyroiditis is now the generally accepted name of this disease, synonyms used formerly included: de Quervain's thyroiditis, granulomatous thyroiditis, giant cell thyroiditis, pseudotuberculous thyroiditis and acute nonsuppurative thyroiditis.

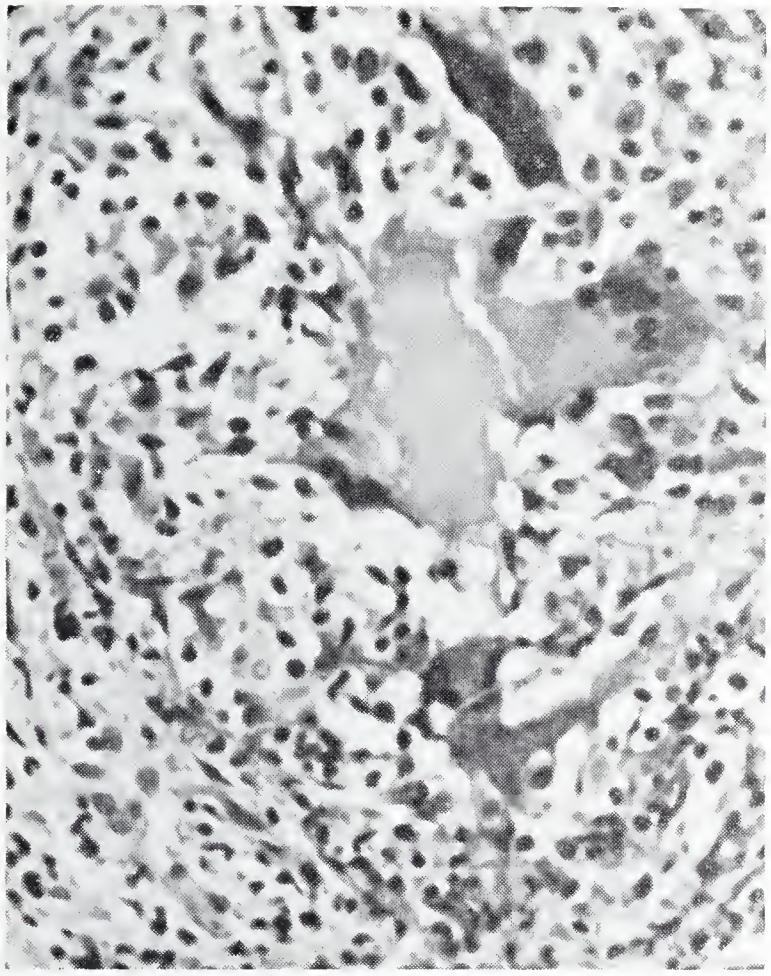
EPIDEMIOLOGY

Two-thirds of the patients afflicted are 30 to 50 years of age. Women are affected 4 times more commonly than men. A relatively rare disease in many parts of the world, it is endemic in western parts of Canada and the United States. At the Presbyterian Hospital in New York City between 1936 and 1952, SAT composed 0.5 to 2.0% of all thyroid diseases seen including hypothyroidism.

THE PATHOLOGICAL PICTURE

On surgical removal, the affected gland can usually be dissected free of its capsule and the surrounding strap muscles of the neck. One or both lobes may be enlarged. Grossly on cut section, one sees pale whitish areas with irregular poorly defined margins. The areas are firm and resemble thyroid carcinoma.

Microscopically one sees lesions of varying pathological development distributed in patches throughout a portion of the gland. The lining epithelium of affected thyroid follicles including the basement membrane is partially or completely disrupted, allowing colloid to seep into the interfollicular space where varying degrees of inflammatory reaction and fibrosis may occur. Mononuclear cells infiltrate the damaged follicles; then giant cells — many of them containing ingested colloid — form and group themselves around masses of residual colloid within the remnants of the follicles. Other follicles may contain neutrophils or radially arranged spindle-shaped cells. Thus the damaged follicle gradually tends to be replaced by a granulomatous structure containing no colloid.



Photomicrograph 400x magnification shows a single follicle involved with the typical abnormalities of SAT. Note the complete disruption of the follicular lining and the absence of follicular epithelium. The remaining colloid is surrounded by mononuclear cells, giving the picture of a pseudogiant cell. The remnant of the follicular space is involved by mononuclear cells. The interstitial tissue evident in the corners of the photograph show marked edema and cellular infiltration as well.

ETIOLOGY

Although rigorous proof is lacking, circumstantial evidence points to a viral etiology for SAT:

1/ Out of 90 patients with confirmed SAT, Volpé et al found 32 patients to have significant changes in titres of antibody to Coxsackie, Influenza, Adenovirus, Mumps or Echo group viruses. In this same study, positive viral cultures could be obtained only for mumps virus in 2 cases. Viral inclusion bodies have never been demonstrated in sections of affected thyroid gland. Other workers have also reported the following viruses in association with the disease: the common cold, measles, infectious mononucleosis, cat scratch fever and Q fever (*Coxiella burneti*).

2/ An acute upper respiratory infection often precedes the onset of SAT by several days.

3/ SAT may occur at the time of specific viral epidemics.

4/ During the acute course of SAT, the patient suffers fever and other systemic manifestations suggestive of a viral disease without neutrophilia.

5/ Patients with SAT usually recover completely in weeks or months, again similar to the course of many viral diseases.

Volpé suggests that SAT could "represent a stereotyped thyroidal inflammatory response to *any one* of a variety of viruses."[8]

PATHOGENESIS

Damage to the thyroid follicular epithelium results in 2 abnormalities of gland function:

1/ Reduced synthesis of thyroid hormones (T4 and T3). Thus the radioiodine uptake is very low. Exogenously administered thyrotropic hormone (thyrotropin or TSH) may increase the radioiodine uptake of an acutely affected gland but this response is usually subnormal.

2/ Stored hormones and abnormal iodinated materials (non-calorigenic iodinated peptides and thyroglobulin moieties) leak into the circulation. Thus in the early stages of the disease, serum Protein Bound Iodine (PBI) levels (representing the total of T4, T3 and abnormal iodinated materials) increase markedly; whereas, serum Butanol Extractable Iodine (BEI) levels (representing for the most part only T4 and T3) rise relatively less if at all. It is this leakage of stored hormones that accounts for the signs and symptoms of hyperthyroidism in the earlier stages of the more severe cases of SAT. Assuming that the patient has not recently ingested large amounts of inorganic iodide (as in cough medicines) or of organic iodine (as in x-ray contrast media), a recent relatively greater increase in PBI over BEI in the presence of clinical evidence of hyperthyroidism and/or thyroid gland discomfort is strongly suggestive of SAT.

The normal thyroid gland contains enough stored, preformed hormones to maintain the body in a state of euthyroidism for 2 months. As noted above, the disease process of SAT disrupts hormone synthesis in the part of the gland it affects. With time the diseased portion of gland will regenerate and its follicles function normally once again. However, if the disease process is very severe and affects the larger part of the gland, the gland's store of preformed hormone will have been exhausted before enough of the glandular tissue will have returned to normal function, and a temporary period of hypothyroidism will result. SAT rarely leads to permanent myxedema, and less severe cases do not go through a stage of hypothyroidism.

The presence of circulating anti-thyroid auto-antibodies can be detected in a minority of cases of SAT (42% of 71 cases studied by Volpé). These antibodies appear several weeks after the clinical onset of the disease, reach a low or moderate titre, and persist for several months only. In SAT thyroid auto-antibodies are probably the result rather than part of the cause of the disease process. A self-perpetuating auto-immune process is not seen to begin. Clinically two tests are used for detecting thyroid auto-antibodies:

1/ Tanned Red Cell Agglutination test (TRCA test) — detects antithyroglobulin.

2/ Complement Fixation test (CF test) — detects antibodies directed against the intracellular microsomal component of thyroid cells.

CLINICAL COURSE

The patient's history usually does not include a preceding goitre. The course of SAT may be thought of as occurring in 3 phases: Indolent Phase, Acute Phase and Recovery Phase.

1/ *Indolent Phase*

This phase lasts about 2 weeks and is characterized by easy fatiguability. It is often preceded by a non-specific upper respiratory infection of presumable viral etiology.

2/ *Acute Phase*

This phase may last from a few days to 3 months, but generally from 2 to 6 weeks.

The classical local symptoms of a severe case of SAT include progressive swelling and tenderness of the thyroid gland with pain radiating to the ears, jaws or occiput and sometimes frank dysphagia with a tight or choking sensation in the neck. On examination, the overlying skin may be warm and red. On palpation, the gland demonstrates diffuse or nodular enlargement no more than 2 to 3 times normal size. The gland consistency may be anywhere between firmness and stony hardness. Tenderness may be found initially in both lobes or one lobe; with time, tenderness may "creep" from one lobe across to the other.

The classical systemic signs of a severe case of SAT include extreme lassitude, weight loss, fever as high as 104 degrees F., occasional chills and night sweats and the signs of hyperthyroidism: nervousness, insomnia, heat intolerance, excessive sweating, flushed facies, tachycardia, wide pulse pressure, tremor, headache and myalgia. Actually, the number of cases which demonstrate obvious hyperthyroidism during the acute stage of their disease is a minority. Most cases are milder and present with varying degrees of thyroid enlargement, pain and tenderness with fever but few if any systemic signs of hyperthyroidism. A mild case may present as a firm goitre simulating thyroid carcinoma.

3/ *Recovery Phase*

In the uncomplicated case, body temperature returns to normal over several days or weeks, thyroid pain and enlargement subsides over 1 to 3 months, and normal thyroid function is re-established.

About one-fifth of all patients have repeated exacerbations after remissions caused spontaneously or by treatment. However, after several months these patients are symptom free and late recurrences are rare.

One-quarter of all cases (usually in those who have suffered a more severe Acute Phase) develop transient hypothyroidism lasting weeks to months from which almost all recover spontaneously. Rarely, permanent hypothyroidism ensues if inflammation of the gland has continued to smoulder over about a year's time.

LABORATORY FINDINGS IN SAT

The results of important tests in SAT have been presented in tabular form below as they vary with the phases of the disease.

↑ Means moderate elevation; ↑↑ means greatly elevated; ↑→ means mild or no elevation.

	Acute Phase	Recovery Phase	Normal Thyroid Function
ESR	↑ ↑ (a)	↑	normal
white blood count	↑→ (b)		normal
BMR	↑→ (c)		normal
PBI	↑ ↑ (d)	normal - - (subnormal)(e)	- - - normal
BEI	↑→	(subnormal) (e)	normal
24 hour radioiodine uptake	usually near zero (f)	normal - supernormal (g) - normal	
TRCA test (for antithyroglobulin)	positive in less than half of cases		

(a) Average ESR during Acute Phase is 80 mm./hour.

(b) Occasionally lymphocytosis is noted.

(c) Basal Metabolic Rate (BMR) is elevated in many cases.

(d) Note the characteristic discrepancy between PBI and BEI levels during the Acute Phase.

(e) PBI and BEI levels may be temporarily at hypothyroid levels if the gland's colloid is depleted before its function recovers.

(f) During the Acute Phase, radioiodine uptake response to exogenous thyrotropin is subnormal or nil. One must remember that an abnormally low radioiodine uptake may be caused by the ingestion of a large quantity of iodine — even the iodine found in cough medicines taken for a sore throat, which condition is itself part of the differential diagnosis of SAT.

(g) During the Recovery Phase the thyroid is under maximal stimulation by endogenous thyrotropin as it repletes its store of hormones.

DIFFERENTIAL DIAGNOSES OF SAT
(Given in descending order of frequency)

1/ *Pharyngitis*. The physician may dismiss the patient complaining of fever and discomfort in the neck as having a pharyngitis caused by the Streptococcus, the Staphylococcus or even by Infectious Mononucleosis and prescribe an antibiotic. This diagnostic error could be avoided by simple examination of the throat, palpation of the neck and by performing a white count; these simple investigations should alert the clinician to the possibility of the less common diagnosis of SAT.

2/ *Acute Hemorrhage* into a pre-existing degenerated nodule of non-toxic nodular goitre.

In this condition there is often a history of goitre with one or more nodules. The onset of fever and thyroid pain is sudden and the ESR is raised only mildly if at all. Needle biopsy clarifies the diagnosis.

3/ *Hashimoto's Disease*. Acute Onset or Acute Exacerbation. There is usually a previous history of thyroid disease. Hashimoto's Disease affects the gland more diffusely than SAT. The radioiodine uptake may be normal or raised, and the ESR elevation is less than that of SAT. The diagnosis is suggested by a high titre of thyroid auto-antibodies.

4/ *Acute Pyogenic (Suppurative) Thyroiditis*. This illness is sudden in onset without a premonitory period. There may be a history of trauma or of septic focus elsewhere. In contrast to SAT, Acute Pyogenic Thyroiditis shows greater inflammatory reaction in tissues adjacent to the thyroid; the white count is far higher; and the radioiodine uptake is usually normal.

Rarely, cases of Graves' disease in the acute phase suffer thyroid pain. Globus hystericus is another cause of discomfort in the throat. In later phases of SAT, one must entertain the differential diagnoses of nodular (adenomatous) goitre, thyroid adenoma or carcinoma, and permanent myxedema.

TREATMENT

The aim of presently known therapies for SAT is limited to the relief of signs and symptoms. Rest and fluids are supportive therapy for SAT as for any febrile illness. The pain and perhaps the inflammation of mild cases is adequately relieved by acetylsalicylic acid; daily divided doses of 4 to 5 grams are given during the entire inflammatory stage and for several weeks thereafter. Moderate and severe cases are best treated with corticosteroids. These agents suppress the clinically observed severity of the inflammatory process but do not appear to shorten the time course required for return of normal gland function as monitored by the radioiodine uptake. Corticosteroids must be given until the underlying disease process has ceased to be active or symptoms will recur. A completely suppressive dose in the order of Prednisone 40mg. (10mg. q6h) is given initially. If the dose is adequate the thyroid will no longer be painful within 24 hours and the elevated ESR will rapidly decline towards normal. Indeed the ESR is a useful indicator of the inflammatory process; the ESR will be seen to rise during an exacerbation before it reaches symptomatic proportions. The suppressive dose of Prednisone e.g., 40mg. daily, is tapered to zero over perhaps 4 weeks. If symptoms recur, the dosage of corticosteroid should be returned to that which relieved symptoms, and maintained for several days before beginning to taper the dosage once again. The dosage and its time course must be titrated to the clinical response. It has been suggested that recurrences following corticosteroid withdrawal can be avoided by giving the corticosteroid in suppressive doses until the radioiodine uptake has returned to supernormal or normal.

In those patients who suffer repeated exacerbations, administration of thyroid hormone following but not during the initial inflammatory (acute) phase has often prevented recurrences by an unknown mechanism. Thyroxine 0.2 - 0.3 mg. per day or triiodothyronine 75 to 125 mg. per day is given several months after all symptoms have ceased, and then the dosage is tapered to zero over 3 months.

For patients with very severe symptoms x-irradiation along with corticosteroid therapy is sometimes helpful. Volpé has found 100 rads per day for 3 to 4 days to be the optimal dosage. Thyroidectomy for treatment is contra-indicated since complete recovery is the rule. Subtotal thyroidectomy done as a diagnostic procedure is indicated when there is clinical suspicion of thyroid carcinoma. Antibiotics, intramuscular thyrotropin and antithyroid drugs are of doubtful value. Thyroxine may have to be given for the relief of temporary hypothyroidism associated with severe cases.

ACKNOWLEDGEMENTS

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Cyclic AMP

H. D. Strauss, B.Sc., 7T2

In 1956, Rall, Sutherland and Berthet were studying the effect of epinephrine and glucagon on liver phosphorylase, an enzyme previously found to be the rate-limiting step in converting glycogen to glucose. Using liver homogenates fortified with ATP and Mg^{++}, phosphorylase activation upon addition of these hormones was observed. However, in supernatant fractions of the homogenates (which contained the enzymes of the phosphorylase system), the hormones were ineffective. When they were added to the particulate debris (containing membrane components), a heat-stable factor was formed, which could then activate the supernatant phosphorylase. This factor was subsequently identified as adenosine 3′, 5′-monophosphate (cyclic AMP) shown in Fig. 1.

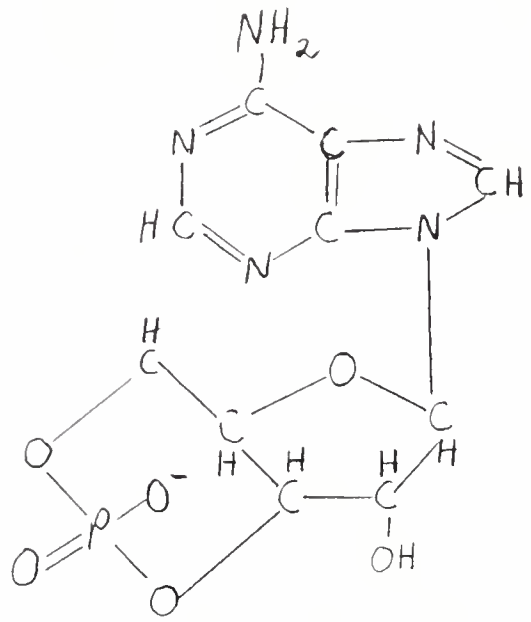

Fig. 1. 3′, 5′ — cyclic AMP

All mammalian tissues (except erythrocytes), many invertebrates, even bacteria contain a membrane-bound enzyme, adenyl cyclase, which acts on ATP to form cyclic AMP and pyro-phosphate. The breakdown of cyclic AMP is effected by phosphodiesterase. Its activity is modified by a variety of substances as shown in Fig. 2.

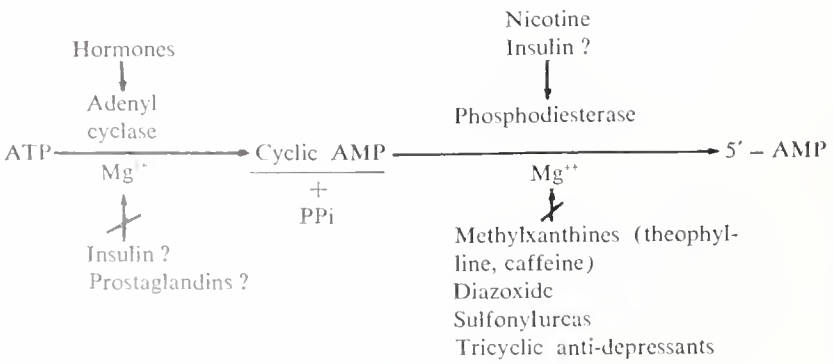

Fig. 2.

THE "SECOND MESSENGER" CONCEPT

The discovery of cyclic AMP ushered in a new era in endocrinology. Many hormones were found to stimulate the production of cyclic AMP, and it in turn was discovered to influence a great variety of metabolic and physiologic processes. In view of this, Sutherland and his colleagues formulated a general hypothesis of hormone action, known as the "second messenger" concept: A hormone ("first messenger") interacts with the surface of the target cell to produce cyclic AMP ("second messenger"). The "deputy molecule" (Tepperman) can then react with intracellular or membrane-bound proteins to direct cellular processes. These may be synthesis of new hormones ("third messengers"), activation or inactivation of rate-limiting enzymes, de-repression of genes resulting in new protein synthesis, alterations in membrane permeability, or states of electrical activity.

The mechanism by which cyclic AMP may effect these changes will be discussed in a later section.

It may well be asked that if a substance can have such a myriad of effects, and can itself be influenced by different hormones, how can one explain the specificity of hormone action? Indeed, some authors have thrown disbelief on the physiological significance of such a substance, surely the devil's messenger. The answer is twofold. First, different target cells respond to different hormone stimuli. For example, adrenal cortical adenyl cyclase is activated by ACTH but not by glucagon, whereas the liver responds to glucagon but not to ACTH. Adipose tissue responds to both (and a number of others as well). The mechanism of this discriminant function will be considered later. Secondly, cyclic AMP affects only the cell in which it is produced, partly because it does not diffuse readily across membranes, and partly because it is rapidly inactivated by phosphodiesterase. Furthermore, different cells have different enzyme systems. This explains the variety of responses in different cells that the same initial event, an alteration in the intracellular level of cyclic AMP, may produce.

The second messenger concept lends itself readily to a description in terms of electronic analogues. Thus the adenyl cyclase system can be viewed as performing the functions of a discriminator of environmental signals and of a signal generator. It is essentially an information transducer, decoding messages concerning the state of the whole system, to modify the functions of individual components. It also has the property of signal amplification since many molecules of cyclic AMP are produced in response to one molecule of hormone. If one accepts the view of hormones as bits of information as first proposed by Huxley in 1930, then cyclic AMP would qualify as an intracellular hormone.

What then, are the criteria to be satisfied for a hormone to act via a second messenger?

(1) The hormone, when added to target tissue, must produce a measurable change in intracellular concentration of cyclic AMP.

(2) This concentration change must precede the metabolic response.

(3) The dose-response relation should be orderly regardless of whether one measures a change in cyclic AMP or metabolic responses.

(4) Exogenous cyclic AMP or analogues should mimic the action of the hormone on the intact cell.

(5) Phosphodiesterase inhibitors such as methylxanthines should potentiate the effect of hormones.

The fourth condition is often difficult to achieve because of poor penetration and rapid inactivation of cyclic AMP. This problem can be circumvented by the use of analogues, especially N^6-2′-0-dibutyryl cyclic AMP, which penetrates cells more readily and is relatively resistant to phosphodiesterase.

THE EFFECTS OF CYCLIC AMP

As mentioned above, cyclic AMP has been discovered to mediate the actions of many hormones and thereby play a pivotal role in the regulation of a diversity of physiological processes. A detailed discussion of each of the effects of cyclic AMP listed in Table 1 would clearly be beyond the scope of this paper. Accordingly, we shall limit ourselves to the following: (a) carbohydrate metabolism, (b) lipid metabolism, (c) steroidogenesis.

(a) *Carbohydrate Metabolism*

In liver and muscle, glycogen synthesis and degradation follow separate pathways, the former controlled by the activity of glycogen synthesase (UDPG-transferase), the latter by phophorylase. Both enzymes exist in an active and inactive form. The inactive phophorylase (dephosphophosphorylase in liver or phosphorylase b in muscle) is converted to active phophorylase (phosphorylase a in muscle) by the addition of phosphate. This reaction is catalyzed by the enzyme phosphorylase kinase, stimulated by cyclic AMP. By contrast, active glycogen synthetase I (glucose-6-PO_4 Independent) is rendered less effective by phosphorylation to glycogen synthetase D (i.e., the G-6-PO_4 Dependent form)). The enzyme involved in this inactivation is also stimulated by cyclic AMP. Thus cyclic AMP, while phosphorylating both enzymes, inhibits one and stimulates the other. This reciprocal action results in increased glycogenolysis. Insulin lowers the tissue level of cyclic AMP (by an effect that may or may not involve adenyl cyclase or phosphodiesterase) and therefore promotes glycogen synthesis. Fig. 3 illustrates these reciprocal effects.

It should be noted that in electrically stimulated muscle, phosphorylase activation does not require cyclic AMP, but follows Ca^{++} release (as Posner, Stern and Krebs (1965) have shown). The obvious suggestion is that Ca^{++} may act as "second messenger" in response to nerve stimulation as much as cyclic AMP acts in epinephrine-treated muscle.

TABLE 1: ACTIONS OF CYCLIC AMP

Action	Change in Activity or Rate	Tissue	Agents acting as "first messenger"
ENZYME ACTIVITY			
Phosphorylase	↑	Liver, muscle	Epinephrine, glucagon
Glycogen synthetase	↓	Liver, muscle	Epinephrine, glucagon
Hormone-sensitive lipase	↑	Fat	Epinephrine, glucagon TSH, ACTH, LH.
Protein kinase	↑	Several	Epinephrine, glucagon, ACTH, etc.
Phosphofructo-kinase	↑	Liver fluke	Serotonin
ENZYME INDUCTION			
Tyrosine transaminase		Brain	——
Phosphoenolpyruvate carboxykinase		Liver	Glucagon, epinephrine
Serine dehydratase		Liver	——
B-galactosidase		Bacteria	Glucose
MEMBRANE PERMEABILITY			
To water	↑	Kidney, toad bladder	Vasopressin (ADH)
To phosphate	↓	Kidney	Parathyroid hormone
HORMONE RELEASE			
ACTH, TSH, LH, FSH, GH	↑	Anterior pituitary	Releasing factor (?)
Thyroid hormone	↑	Thyroid	TSH
Insulin	↑	β-cells of pancreas	Glucagon
Calcitonin	↑	Parafollicular cells of thyroid	Ca^{++} (?)
RELEASE OR SECRETION OF NON-HORMONAL SUBSTANCES			
Amylase secretion	↑	Parotid	Epinephrine
HCl secretion	↑	Gastric mucosa	Histamine, gastrin
Fluid secretion	↑	Insect salivary gland	——
Acetylcholine release	↑	Nerve	Epinephrine
Histamine release	↓	Leucocytes	Prostaglandins
HORMONE SYNTHESIS:			
Adrenal steroids	↑	Adrenal cortex	ACTH
Sex steroids	↑	Corpus luteum, ovary, testis	LH (ICSH)
Melatonin		Pineal	Norepinephrine
Renin		Kidney	?
PHYSICAL EFFECTS:			
Contractility	↑	Cardiac muscle	Epienphrine, glucagon
Tension	↓	Smooth muscle	——
Membrane potential	↑	Smooth muscle	——
Discharge frequency	↓	Cerebellar cells	Norepinephrine
Melanocyte dispersion	↑	Frog skin	MSH
Aggregation	↓	Platelets	Prostaglandins

(b) *Lipolysis*

In 1965, Butcher and his colleagues demonstrated conclusively that epinephrine-stimulated lipolysis (breakdown of triglycerides to fatty acids and glycerol) in adipose tissue was associated with an intracellular accumulation of cyclic AMP. Glucagon, ACTH, TSH and LH act similarly. The enzyme involved is a hormone-sensitive lipase, previously shown by Rizack (1964) to be activated

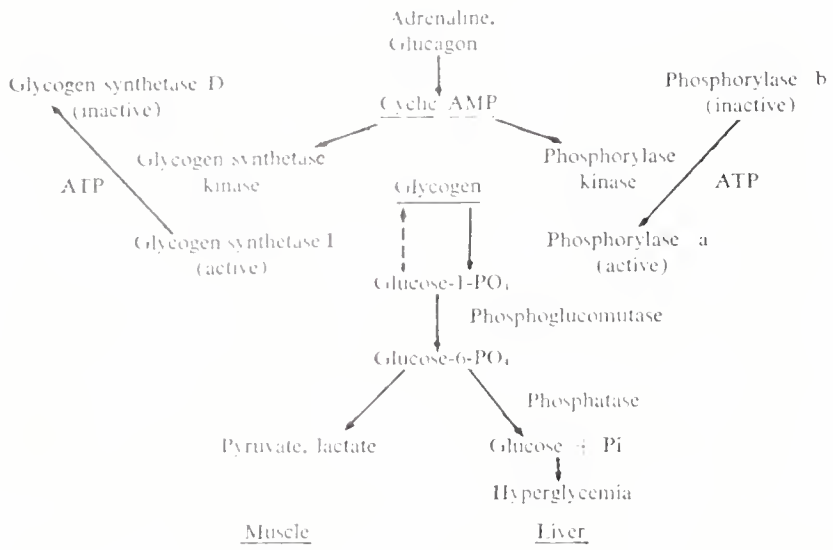

Fig. 3. Reciprocal effects of cyclic AMP on glycogenesis and glycogenolysis.

when cyclic AMP was added to cell-free systems prepared from adipose tissue. These hormones also stimulate phosphorylase in fat, but this effect seems unrelated to lipolysis. Insulin, adrenergic blocking agents, prostaglandin PGE, and nicotine have an anti-lipolytic effect. Nicotine stimulates phosphodiesterase and the adrenergic blockers act at the adenyl cyclase receptor site.

The lipogenic effect of insulin is readily explained on the basis of glucose transport stimulation, for glucose provides: (1) acetyl CoA precursors for long chain acids, (2) glycero-phosphate for esterification, and (3) TPNH via the hexose monophosphate shunt for ethylene bond saturation. It is therefore natural to suppose that the *anti-lipolytic* effect could also be based on glucose transport. However, it was found that insulin blocked epinephrine-stimulated lipolysis in the absence of available glucose, and Jungas showed that insulin lowers fat cell levels of cyclic AMP.

The interaction of prostaglandins and cyclic AMP will be touched upon briefly further on, but for detail the reader is referred to the article on prostaglandins by R. Wald.

(c) *Steroidogenesis*

Haynes (1957) first showed that cyclic AMP was involved in the effect of ACTH on adrenal steroidogenesis. Furthermore, he postulated an attractive mechanism of action based on the assumption that availability of TPNH (required for reductive hydroxylation) was the rate-limiting factor. ACTH-stimulated cyclic AMP would activate phophorylase, followed by glycogenolysis with the production of hexose phosphates. These would force an increased flow of metabolites through the HMP shunt making more TPNH available.

The possibility of an alternative mechanism arose in 1963 when Ferguson discovered that puromycin could block the steroid response to ACTH and cyclic AMP, but not to TPNH. Other protein synthesis inhibitors like chloramphenicol and cycloheximide acting at the translational level (RNA>protein) also blocked the response.

However, Actinomycin D, which acts at the level of transcription (DNA>RNA), did not. The conclusion was that ACTH via cyclic AMP stimulated the synthesis of a protein, which did not require new RNA synthesis. This protein, called "rapidly turning over protein" by Garrow, was postulated in some way to enhance cholesterol side chain cleavage, shown by Hechter and Stone to be the rate-limiting step in steroid synthesis.

A schematic diagram of the effect of cyclic AMP in the adrenal cortex is shown in Fig. 4.

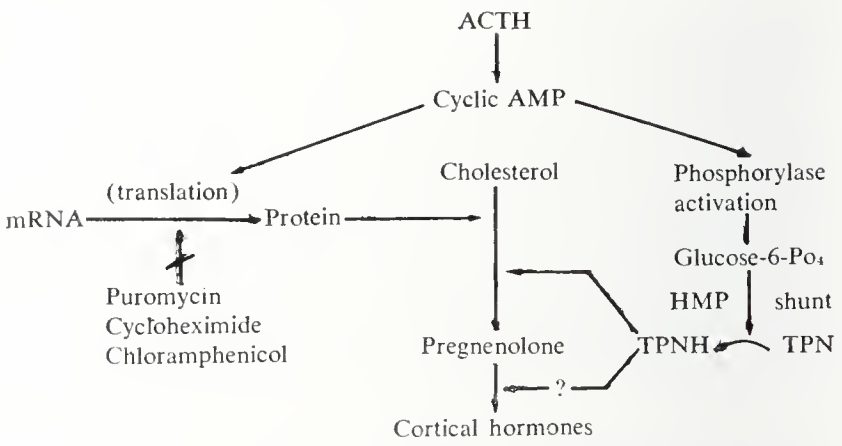

Fig. 4. Possible mechanisms of action of ACTH

CYCLIC AMP AND HORMONE ANTAGONISMS

It has already been noted that insulin lowers levels of cyclic AMP in liver and fat, thereby blocking the effects of epinephrine and glucagon. Insulin, interestingly enough, is a hormone released from one set of cells by cyclic AMP and acts by reducing the level in another. Here is an example in which cyclic AMP appears to be involved in a sort of negative feedback. It is probable that feedback inhibition of a number of hormones is mediated by cyclic AMP, already shown to be the case in the release of FSH and TSH by their respective hypothalamic releasing factors.

The pineal hormone melatonin and α-adrenergic catecholamines also lower intracellular levels of cyclic AMP. This is illustrated in the reversal of the effect of MSH on the dorsal skin of the frog, *Rana pipiens*. MSH, acting via cyclic AMP, causes melanophore dispersion in dermal cells, thus darkening the skin. Melatonin and epinephrine lighten the skin.

The effect of prostaglandins on cyclic AMP are varied. They have been found to increase levels in leucocytes and platelets, yet PGE_1 blocks the lipolytic effects of glucagon and epinephrine, and the action of vasopressin on the toad bladder, by decreasing cyclic AMP. Furthermore, many hormones that cause increased levels of

cyclic AMP also stimulate prostaglandins. It may be that prostaglandins are synthesized as a result of the action of cyclic AMP and would then act as feedback regulatory system, as proposed by Bergstrom, or that release of prostaglandins is a reflection of a more primary event such as activation of adenyl cyclase.

Acetylcholine has been found to lower cyclic AMP concentrations in ventricular myocardium, which may be expected in view of the fact that epinephrine has the opposite effect.

RECEPTORS AND THE MECHANISM OF ACTION OF CYCLIC AMP

To explain the specificity of hormone action via the common pathway of adenyl cyclase activation, different target cells are visualized as bearing membrane receptor sites of differing molecular configuration. It is postulated that the membrane-bound adenyl cyclase system consists of two subunits. A regulatory subunit (the receptor) facing the extracellular space interacts with the hormone. This results in some conformational change, activating the catalytic subunit (the enzyme) facing the intracellular space.

Are there different cyclase systems in tissues which respond to more than one hormone? Although inconclusive, the answer appears to be negative. Fat cells will not respond further upon addition of other hormones, when already maximally stimulated by one.

Various mechanisms of action of cyclic AMP have been proposed, but the one which has received greatest attention is the activation of protein kinases by binding of cyclic AMP. The adenylated kinases may then alter the activity of enzymes such as phosphorylase and glycogen synthetase; or phosphorylate histones, thereby decreasing their activity as gene repressors; or alter membrane permeability by some, as yet undetermined, structural change.

Like the adenyl cyclase system, cyclic AMP-dependent protein kinases consist of two subunits, a cyclic AMP receptor unit, and a catalytic unit. Inactivating the kinase, cyclic AMP binds to the receptor, causing it to dissociate from its complex with the catalytic unit. The latter is freed from the inhibitory effect of the receptor and thus activated.

Another suggestion has been that cyclic AMP may act by releasing Ca^{++}. That Ca^{++} may activate enzymes was mentioned in connection with muscle phophorylase. There is certainly evidence that the positive inotropic effect of cyclic AMP on cardiac muscle is due to increased Ca^{++} fluxes across the sarcolemma.

It is, of course, quite possible that cyclic AMP may act by more than one mechanism, which may depend on the particular response or on the cell type involved.

THE CLINICAL SIGNIFICANCE OF CYCLIC AMP

Although most of the research done on cyclic AMP since its discovery has been of a biochemical-physiological nature, some recent work of clinical import has appeared. The studies of Chase and Aurbach on urinary excretion of cyclic AMP are an outstanding example. Normal humans excrete 2-9μmols of the nucleotide per day, 60% of this being derived from plasma, the remainder from the kidney itself. It was found that the excretion rate was markedly increased in patients with primary hyperparathyroidism, and the excess was of renal origin. However, in pseudohyperparathyroidism, a congenital disease characterized by renal unresponsiveness to parathyroid hormone, reduced urine values were observed. They suggested the use of urinary cyclic AMP levels as a test to differentiate the hypercalcemia of hyperparathyroidism from other causes not related to excess levels of PTH. In the latter, of course, values would not be elevated.

Another result of their work, perhaps more exciting in its implications, has been the demonstration that pseudohyperparathyroidism involves some defect in the adenyl cyclase system. This has led to the speculation that other diseases of target tissue unresponsiveness involving a similar defect would be found. Indeed, Cesari and Tuft have suggested that the basic defect in diabetes mellitus may be the reduced ability of pancreatic β-cells to produce cyclic AMP, with resulting failure of insulin release. Other possible candidates might include some forms of glycogen storage disease, idiopathic hypoglycemia, or athyrotic cretinism. This is certainly a fruitful area for further investigation.

In 1968, Szentivanyi described a new theory of the atopic abnormality in bronchial asthma. In short, a defective effect or mechanism for β-adrenergic action in bronchial tissue was postulated. Although direct experimental evidence is lacking, a relative deficiency of adenyl cyclase may be involved. This would explain the epinephrine tolerance seen in some asthmatics, as well as the therapeutic effectiveness of aminophylline.

In 1970 Abdulla and Hamadah reported that patients with affective disorders excrete abnormal amounts of cyclic AMP in their urine. In depressed patients the values were low, whereas in manic patients they were high. Furthermore, levels returned to normal upon clinical improvement. A deficiency of cyclic AMP in brain cells was postulated to cause depression. Low levels of cyclic AMP in other tissues could well explain the many somatic symptoms of depressed patients, assuming that depression is really a systemic illness. They also found that the tricyclic antidepressants, such as imipramine, are very potent phophodiesterase inhibitors and obtained evidence to suggest that the pharmacological action of these drugs is mediated via cyclic AMP.

No doubt, further research will implicate the ubiquitous cyclic AMP in many aspects of medicine.

CONCLUSION

Many hormones are known to act via cyclic AMP, a substance widely distributed in the biological world. Its discovery led to the formulation of a new concept of hormone action — the "second messenger" hypothesis. It has provided a unifying theme for endocrinology, laying the foundation for an understanding of information transfer in biological systems. Cyclic AMP seems to have done for endocrinology what DNA did for genetics and biochemistry: it has occupied the attention of a great number of investigators throughout the world for the past decade, and will likely continue to do so. It is almost certain that the study of cyclic AMP will contribute significantly to future developments in endocrinology, and bring man in some small way closer to an understanding of living things.

ADDENDUM

In 1971, Sutherland received the Nobel Prize in Medicine and Physiology in recognition of his work on the mechanisms of hormone action.

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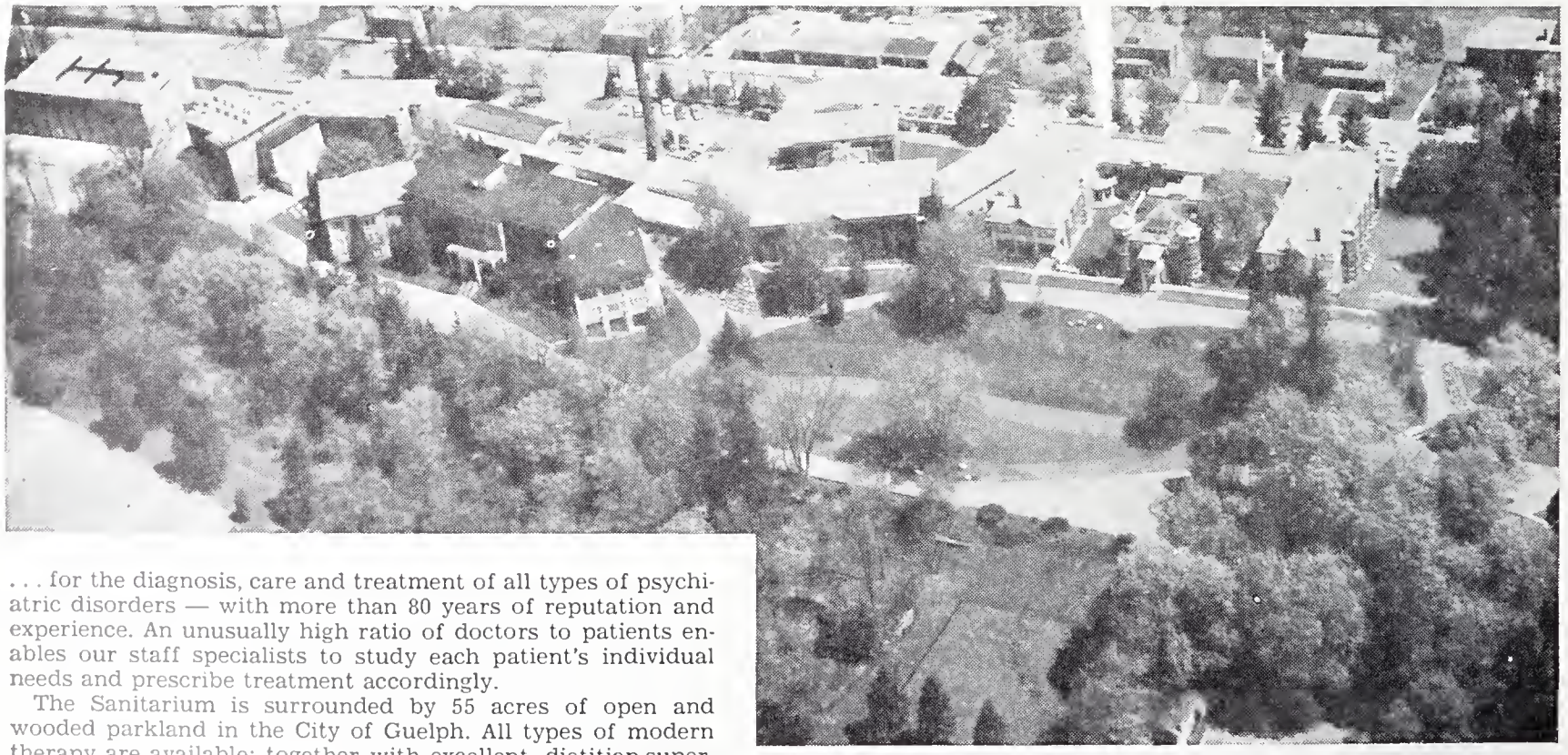

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A Thumbnail Sketch Of The Origins Of The New Curriculum

P. T. Randall, 7T2

Since the Flexner Report of 1910, the University of Toronto Faculty of Medicine has always deemed itself to be among THE medical schools in North America. With the important contributions to medical science of Toronto researchers like Banting and Best, this self-image has been enhanced. But both medical knowledge and medical education have come a long way since 1910, and in particular new ideas and changes in medical education have only really become important in the last twenty years. The University of Toronto introduced its "New Curriculum" in 1969. Whether this revision in undergraduate teaching is a distinct improvement and more in keeping with present thoughts in medical education and with present needs of the potential future doctor is difficult to assess at the moment. An evaluation of the New Curriculum is currently under way. In order to see if the New is an improvement on the Old, let us examine the Old and see why and how the New Curriculum came into being in the first place.

THE OLD CURRICULUM

Before 1969 the curriculum at the University of Toronto was the standard four-year, departmentalized program common to most medical schools on this continent during the middle of this century. Anyone interested in the history of the University of Toronto Faculty of Medicine should refer to the articles by Buehrle[1] and Beatty.[2] Suffice it to say that the curriculum at Toronto was largely unchanged since World War II. While there had been some patching carried out here and there in the program, many of the changes amounted to changes in the titles of certain lectures.

The Old Curriculum, as we shall call the pre-1969 version of Toronto's program, was largely departmentalization, the lectures and clinics being organized by the chairman of the department, who appointed lecturers and clinicians to teach the subject matter. As it turned out, the content of the curriculum was largely unorganized, for few lecturers knew what other lecturers talked about, and one department knew little about what the other departments taught. Thus, on a topic like tuberculosis, each of the Departments of Medicine, Surgery, Pediatrics, Bacteriology, Pathology and Preventive Medicine might have something different to say, and each might say it at a different time during Second and Third Years. A similar situation would apply in the teaching of a topic such as peptic ulcer. In this way, there was a lot of duplication and overlap in the didactic discussion of clinical sciences. At the same time, responsibility for a given topic could be "sloughed" to another department, and in this manner the curriculum was weakened by poor coverage of a topic.

Another way in which the Old Curriculum was unorganized was in respect of teaching clinics. These sessions were, of course, run by the clinical departments. The subject matter for an eight-week series of clinics in Medicine was up to the whim and fancy of the clinician involved, who, if he was an endocrinologist, might tend to emphasize teaching on patients with endocrine disease, while ignoring patients whose primary disease lay in other body systems. Somehow, during his years of clinical instruction, the medical student was hopefully exposed to a broad number of subject areas in Medicine. Although this method of organizing clinics did take advantage of the interesting patient material available at any one time, it was rather hit-and-miss in attempting to cover the subspecialty areas of Medicine.

The problem in particular with fourth year in the Old Curriculum is rather pessimistically summed up in this excerpt from the "Probe":[3]

> "What is it like to be in Fourth Year Meds? Well, first of all, you don't even feel like part of a university. You never even go near the Campus. You spend various odd assorted hours peering over residents' shoulders. Peering over surgeons as they open an abdomen (or, worse, pulling on retractors). Peering over medical residents' shoulders as they read charts. Peering over O.B. residents' shoulders as they apply forceps and pull. Peering over pediatricians' shoulders as they look at some two-year-old's tonsils. You never *do* anything. And worse, you never *belong*. You are lost, wandering about lost. One week on orthopedics, one on neurosurgery, etc., etc. Despair envelops you. You don't even see your classes any more. Just impersonal residents and staff-men that recognize you as a medical student and don't even know your name. Not very pleasant or even healthy for that matter. Usually just another body in white trailing the procession on ward rounds. Oh for a clinical clerkship."

It seems that the old fourth year was a let-down (a "reading year" as one student described it) after the hard work of third year. Fourth-year students were not part of "the clinical team" and had no night or weekend duties, except for their month on Obstetrics and Gynecology. They were there merely to "observe what was going on" on the ward, but were unnecessary to its satisfactory functioning. There were occasional chores to do: usually scutwork sloughed by the interne. Since the students changed hospitals every eight weeks, it was hard for them to feel at home in one place, and it was hard for the staff to get to know them. Although there was one central lecture per day for the whole class, it was rarely attended by more than 25% of the students.

THE EVOLUTION OF THE NEW CURRICULUM

By the mid-1960's, the University of Toronto's medical curriculum had received no major overhauling in twenty years, having been revised only in a patchwork manner from time to time. Apparently there was a feeling

among some of the staff that something had to be done about the Old Curriculum and the complacency surrounding it.

In 1962, Dr. W. Oille conducted a survey of the medical course based on comparisons with other schools he visited in the United States and the United Kingdom. At the Guild Inn in 1963, the Faculty Council Study Meeting discussed the basic aims of the Faculty:

> "There was virtual unanimity to the effect that our goal at the end of undergraduate training should be the production of a basic doctor who, with a minimum of two years' further training, could then begin to serve the health needs of the community as a practitioner or proceed with further specialist training, and that our aim should not be to direct a medical student into any particular branch of practice."

With this philosophy in mind, let us digress for a moment to mention a few events taking place at a "supra-Faculty" level.

The Provincial Government of Ontario wanted, as it always does, more doctors in the province. It also was interested in turning Sunnybrook Hospital, then under the Department of Veterans' Affairs, into a general, teaching hospital within the University of Toronto. The Borden Committee (Mr. Henry Borden was chairman of the University of Toronto Board of Governors) negotiated with the Government on the acquisition of Sunnybrook Hospital, in return for increasing the Faculty of Medicine's enrolment from 150 to 250 students per medical year.

Reacting to these proposed changes, Faculty Council members requested money for a new Medical Sciences Building, and for building and expansion programmes in the hospitals, in order that the medical school be able to handle the increased enrolment. Thus, the plans for a new medical building on campus, designed to handle classes of 250 students, went ahead in 1964-65, unfortunately well before the New Curriculum was designed.

In 1965 a concept evolved with respect to the increased enrolment, such that four semi-autonomous medical schools would be established within the University, in keeping with the expansion plans for improved facilities for teaching and research. The four such "schools" would be located at the Toronto General Hospital, the Toronto Western Hospital, St. Michael's Hospital, and the newly acquired Sunnybrook Hospital. Although this scheme was kept in mind for several years during the planning of the New Curriculum, it never materialized, partly because of philosophical reasons, and partly because the money promised for teaching-hospital renovation and expansion was not forthcoming.

With this background in mind, let us return to the growth and development of the New Curriculum. In November 1965, Dean J. D. Hamilton asked each of the clinical departments to set up a Curriculum Committee to evaluate the purpose and the methods of its teaching, and the integration of same with that of other clinical departments. Recommendations were to be made to a Clinical Curriculum Committee, whose task it was to co-ordinate efforts toward changing the curriculum. The Chairman was Professor K. J. R. Wightman, and the members were: Dr. W. E. Boothroyd, Dr. I. M. Hilliard, Dr. J. C. Laidlaw, Professor A. C Ritchie, Dr. N. A. Watters, Dr. N. T. McPhedran, Professor W. Paul, Dr. J. H. Ebbs, Dr. E. A. Sellers and soon-to-be-Dean A. L. Chute. Of course, the basic science departments were doing similar things.

By March 1966 ideas for a different sort of programme were taking shape. The decentralized plan of four separate clinical programmes going on in the big hospitals was discussed, as was a change to block teaching instead of having several unrelated topics at once. The introduction of audio-visual aids, with an inter-hospital television network, taped lectures, and a film-tape library was envisaged. The problem of integration, i.e. teaching the medicine, surgery and pathology relevant to one organ system, was talked about. The Faculty also considered the role of student evaluation, and multiple-choice and composite examinations.

In the clinical years, it was felt that, with the decentralized system, the laboratory aspects of clinical medicine would be taught by clinical people in multidisciplinary laboratories within the hospitals. Individual study space would be provided for the students, as well as lab facilities close to the wards where routine blood and urine tests could be performed. The area of laboratory medicine might be a good place to attempt to solve the perennial problem of bridging the gap between basic and clinical sciences; e.g. by involving basic science instructors in the teaching at the hospitals.

It was recommended that the final year of medicine be a clinical clerkship, twelve months long. The students would live in the hospitals, and become active members of a clinical team, with responsibilities for patient care. As long as service duties did not hinder learning, it was felt that the greater contact with the hospital staff and opportunity for more practical experience would be an improvement on the old fourth year. Three months of the clerkship would be set aside for electives, primarily in some areas of laboratory medicine. In addition, no hospital where there were clerks should have junior rotating internes; clerks would be at a hospital for the whole year. This program depended on the Ontario Hospital Services Commission to provide $1200 in lieu of summer earnings. The Ontario College of Physicians and Surgeons allowed that a satisfactory clerkship would take the place of rotating interneship, thus potentially shortening the period of specialist training.

In 1967-68 the clinical clerkship was begun on an experimental basis with sixteen members of the final year class at the Wellesley Hospital.

It might be worth while at this point to mention some of the influences that came to bear on the development

of the New Curriculum. Drs. Sellers and Laidlaw visited Harvard University and Dr. Boothroyd visited the University of Rochester. Accordingly, the programmes of these leading American schools were examined by the Committees. In addition, Dr. W. R. Drucker, a former staff member at Case - Western University, was involved in planning in Toronto, using some of the ideas and philosophies of his famous former employers. Finally, it might be said that the influx of younger, full-time clinicians during the mid-1960's helped in the curriculum change, for these were people with heavy commitments to the University, to teaching and research, who also had more time to devote to curriculum planning than did part-time staff.

In the summer of 1966, a "White Paper on the Clinical Curriculum"[4] was produced, outlining the general plan of the curriculum and three possible programmes for the clinical curriculum.

The first year and a half of the medical course would be spent by the 250 students at the Medical Sciences Building on campus, learning a basically interdigitated course in physiology, biochemistry, and pharmacology taught as systems, with general pathology, anatomy, behavioural sciences, and other basic sciences taught as separate topics.

The next year and a half of the course would be the clinical part, based at the four major teaching hospitals ("clinical schools"). The final year of the course would consist of the clinical clerkship.

The first suggestion for the clinical curriculum was that it be a modified departmental approach, with integration among departments to provide a co-ordinated presentation on specific topics, e.g. neoplasms of the gut would involve radiology, pathology, surgery, and so on, at the same time. This method, based on existing structures and organization, would be easiest to implement and run. Besides, "the quality of the training we produce will depend less on the curriculum we use than on the enthusiasm and imagination which the teachers generate."

The second proposal was a system-based curriculum, run by "system committees", each consisting of members of departments with an interest in the respective systems. The second half of second year would consist of Fluid and electrolytes, Blood diseases, Endocrinology, Special senses (ENT and ophthalmology), Injuries to tissue (burns, fractures, wounds, gangrene), Infectious diseases, Allergic diseases, Anesthesia, and Public health. Third year would consist of six blocks of five weeks each: the Cardiovascular system, Respiratory system, Nervous system, Musculoskeletal system and skin, Gastrointestinal system, and Urinary and reproductive systems.

The advantages of this plan were felt to lie in the autonomy the Systems Committees and hospitals would have, allowing for variety in teaching techniques. There would not be omissions or overlap in content if the Systems Committees were effective. The disadvantages involved the heavy student load during any one system, unless the class were divided into six groups to rotate through the systems. This would cause repetitive work for the teachers. This plan also ignored geographical strengths and weaknesses in various systems.

The third proposal for the clinical curriculum was a combined approach; i.e. the course would be divided into two parts, a systemic segment (didactic lectures, seminars and demonstrations) and a departmental segment (clinics and hospital laboratories). The departmental time would be allotted depending on the needs of the system. Students would be allotted to medical wards, surgical wards, and OBG wards, etc., and would see whatever patients happened to be on the ward. This method would review and anticipate the content of the systemic segment, and would take advantage of the interesting clinical material in hospital at any one time. Thus, this plan attempted to capitalize on the advantages of the first two proposals. Its disadvantages were similar to those of the second proposal, and it required a very large teaching staff to run both systemic and departmental segments simultaneously.

The proposals contained in this White Paper formed an important part of the discussion held in October 1966: the Guild Inn Curriculum Meeting.

The discussion at this meeting included many topics and issues germaine to the New Curriculum in particular and to medical education in general. One problem concerned the co-ordination of the clinical and basic science parts of the curriculum, the introduction of clinical material into the preclinical period, and the continuation of basic sciences in the clinical period. It was felt that these items should be explored.

Another important area concerned electives and the provision of free time. Many staff members felt that the Old Curriculum was too crowded and structured with no free time, and offered little opportunity for the student to explore possible career choices and to pursue his own interests. Accordingly, it was suggested that the clinical clerkship have a block of elective time. Elective periods in the earlier years could be either one day per week or a block at the end of the year.

At this time, the concept of having several clinical schools, each taking a group of students for at least one year, was still in vogue. Also, the introduction of teaching in behavioural sciences was favoured.

With the discussions that took place at the Guild Inn and with the meetings of committees held in the ensuing months, it became clear that systems-based interdepartmental teaching should be instituted in the first three years of the course and that a twelve-month clinical clerkship constitute fourth year. The content of this New Curriculum, and the objectives with which it was planned, were set out in "A Proposed Plan of an Educational

Programme"[5] in December 1966 by Dean A. L. Chute and Drs. E. A. Sellers, J. C. Laidlaw, W. R. Drucker and J. W. Steiner.

The original idea that there be four semi-autonomous schools was discarded because of the wide variation among institutions in academic strength in many areas, and because of the difficulty in creating a small number of schools from ten teaching hospitals. In addition, duplication of equipment and competition among schools for staff and money were felt to be detrimental. Finally, the separation of such hospital groups was thought to be a potentially divisive rather than integrative force within the medical school.

By early 1967, the New Curriculum was certainly in existence on paper, and ready to begin being planned in earnest by systems committees and period co-ordinators.

Also in 1966-67, students were involved for the first time in the discussions taking place. Hopefully their presence and activity was some stimulus for the staff to "take a look at things", e.g. examinations. Certainly students did provide impetus and suggestions for change, as well as feedback when the New Curriculum was finally introduced. A humorous assessment of the brand New Curriculum was supplied by four students in "Daffydil 1968."[6]

CONCLUSION

The transition to a new type of programme has not been easy. It has involved tremendous work on the part of many, many people. It has trodden on the toes of the departments in the Faculty, and deprived them of their age-old prerogatives in the composition of undergraduate teaching. But, more importantly, it has shaken up this medical school, it has decreased complacency and offered the capacity for change, it has got people thinking about the curriculum and what they're doing in it, and it has involved large numbers of the "grassroots" staff. Surely these latter elements are a good thing.

Whether or not the New Curriculum itself is a good thing and a definite improvement on the Old is a difficult question. Perhaps the evaluation currently under way will give us some answers. Perhaps we have indeed "come full circle"[7] in medical education.

ACKNOWLEDGEMENTS

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Grand Round Quiz - Questions

Resident - Endocrinology
Dr. T. C. Monchesky,

(1) *A forty-year-old male presents to his family physician with headaches and a tendency to bump into objects on his left side. He has also noticed that he has been recently scraping the left side of his car when driving into his garage. Skull x-rays show an enlarged sella.*
Which of the following is the earliest test to be abnormal in pituitary compression by a tumour.
(a) T.S.H. assay.
(b) I^{131} uptake.
(c) Metyrapone test.
(d) Growth hormone response to insulin induced hypoglycemia.
(e) Low F.S.H.

(2) *Which of the following is the earliest symptom to present ?*
(a) Decreased libido and potency.
(b) Loss of tanning ability.
(c) Shortening of the bones and shrinking of the hands and feet.
(d) Cold intolerance.
(e) Postural hypotension

(3) *A thin twenty-five-year-old male presents with weight loss, polydypsia and polyphagia. Urinalysis reveals 2% sugar and moderate ketones. His FBS is 350 mg.%. Following a trial on an 1800 calorie diabetic diet, his FBS remains at around 200 mg.%.*
How should he be managed?
(a) Continue 1800 calorie diet.
(b) Start Lente insulin 15 to 20 U. q.a.m.
(c) Start on pzI insulin 15 to 20 U. q.a.m.
(d) Start on chlorpropamide 250 mg. O.D.
(e) Start on chlorpropamide 250 mg. O.D. and add DBI-TD if necessary.

(4) *The above patient returned with a skin infection on several occasions.*
Which of the following is true?
(a) All diabetics have an increased tendency to develop infection.
(b) The patient most likely had poor diabetic control.
(c) Infections in diabetes are due to the high blood sugar which provides a good culture medium.
(d) Ketosis is associated with increased infections.
(e) All infections in diabetes are due to poor circulation.

(5) *A thirty-year-old white male presents with a hard nodule in his thyroid gland.*
What diagnosis must be considered?
(a) Subacute thyroiditis.
(b) Hashimoto's thyroiditis.
(c) Thyroid adenoma.
(d) Thyroid carcinoma.
(e) Colloid goitre.

(6) *What is the most valuable test?*
(a) TSH level.
(b) Serum thyroxine.
(c) I^{131} uptake.
(d) Thyroid scan.
(e) PBI.
(f) T3 uptake.

(7) *If the patient is a woman with an elevated serum thyroxine and T3 uptake, an elevated I^{131} uptake, and a scan showing a hot nodule. What is the most likely diagnosis from the list in question No. 5?*

(8) *What is the treatment of choice for the thirty-year-old male if the nodule showed no uptake on scan?*
(a) Surgical removal of the nodule.
(b) Needle biopsy and open surgery if the biopsy shows carcinoma.
(c) I^{131} therapy.
(d) Suppression of the gland with thyroid medication.
(e) External irradiation.

(9) *Match the drugs in column A with the side effects in column B.*

A.	*B.*
(1) Chlorpropamide	(a) Gynacomastia
(2) Potassium Iodide 300 mg. OD	(b) Hyponatremia
(3) Propylthiouracil 50 mg. b.i.d.	(c) Goitre
(4) Reserpine	(d) Pancytopenia
(5) Aldactone	(e) Galactorrhea

(10) *Match the drug or hormone in column A with the closest in column B.*

A.	*B.*
(1) T.R.F.	(a) Increase by dopamine.
(2) Chlorpromazine	(b) Found in pancreatic tumours.
(3) L-Dopa	(c) Galactorrhea due to its presence.
(4) CRF	(d) Depressed growth hormone levels.
(5) P.I.F.	(e) Elevated growth hormone levels.

TRUE OR FALSE
(a) True — True
(b) True — False
(c) False — True
(d) False — False

(11) *Addison's Disease is common in metastatic breast carcinoma/ because the adrenal gland is a common site for metastatic breast carcinoma.*

(12) *Hypercalcemia is not uncommon in metastatic breast carcinoma/ because breast carcinoma not uncommonly produce a parathormone-like substance.*

(13) *All persons with Addison's Disease should be investigated for tuberculosis/ because tuberculosis is the most common cause of Addison's Disease.*

(14) *Birth control pills produce hyperglycemia in a chemical diabetic / because the progestational agents antagonize insulin action.*

(15) *Iodine is used in the treatment of Grave's Disease /because iodine in high concentrations blocks the active transport mechanism for iodide uptake as well as blocking thyroid hormone release.*

(16) *Myopathy is associated with which of the following?*

1. Cushing's Syndrome.
2. Steroid therapy.
3. Hypothyroidism.
4. Hyperthyroidism.
5. Hyperparathyroidism.
6. Addison's Disease.

A. All.
B. All but 6.
C. All but 5 & 6.
D. All but 3, 5 & 6.

(17) *Glucagon is associated with the following effects.*

1. Glycogenesis.
2. Gluconeogenesis.
3. Lipolytic activity.
4. Hyperglycemia.
5. Insulin release.

A. All.
B. All but 5.
C. All but 4.
D. All but 1.

(18) *Insulin is associated with the following effects.*

1. Glycogenesis.
2. Antilipolytic effect.
3. Increase of hormone sensitive lipase.
4. Increase of C-AMP in the adipose cell.
5. Hypoglycemia.

A. All.
B. All but 3.
C. All but 4.
D. All but 3 & 4.

(19) *Successful treatment of adrenal crisis includes the following:*

1. Replacement of sodium and water deficit.
2. Replacement of potassium deficit only.
3. Rapid elevation of circulating adrenocortical hormone level.
4. Only IM injection of 50 mg. cortisone acetate.
5. Infusion of 5% NaC1 solution.

A. If 1, 2 and 3 are correct.
B. If 1 and 3 are correct.
C. If 2 and 4 are correct.
D. If all are correct.
E. If none are correct.

(20) *Acute adrenocortical insufficiency can be precipitated by:*

1. Any form of stress superimposed on chronic adrenal insufficiency.
2. Overwhelming infection.
3. Withdrawal of steroid from patients on chronic steroid administration.
4. Birth trauma.
5. Following idiopathic adrenal vein thrombosis.

A. If 1, 2 and 3 are correct.
B. If only 1 and 3 are correct.
C. If only 2 and 4 are correct.
D. If all are correct.
E. If none are correct.

Grand Round Quiz - Answers

(1) (d) In the natural history of panhypopituitarism secondary to a space-occupying lesion the order of failure of trophic hormone secretion is as follows: GH, gonadotrophins, TSH, ACTH.

(2) (a) Failure of growth hormone secretion in adults has no clinical manifestations.

(3) (b)
All young diabetics should be started on insulin. Ketosis is a contraindication for the use of oral agents.

(4) (b) and (d)
Well controlled diabetics without complications have about the same frequency of infections as the general population. Ketosis decreases the ability of a diabetic to resist infections.

(5) (d)
A male who has a hard thyroid nodule should be considered to have carcinoma until proven otherwise.

(6) (d)
There is a higher incidence of carcinoma in "cold" nodules on thyroid scan. Thyroid carcinoma usually does not bind iodine.

(7) (c)
Hot nodules, i.e. functionally active foci, are more frequently adenomatous than malignant.

(8) (a)
10-20% of hard, cold nodules are malignant!

(9) (1) (b)
(2) (c)
(3) (d)
(4) (e)
(5) (a)

(10) (1) (c)
(2) (d)
(3) (e)
(4) (b)
(5) (a)

T.R.F. has an inverse relationship to P.I.F. Chlorpromazine blocks the release by the hypothalamus of GHRF (NEJM, 1971). L-Dopa stimulates the release of GHRF and PIF blocks the release of CRF. Both ACTH and CRF can be released from bronchogenic and pancreatic carcinomas.

(11) c.
Metastatic breast carcinoma frequently spreads to the adrenal, but rarely produces any effect.

(12) b.
There have only been a very few cases reported of breast carcinoma producing a parathormone-like substance.

(13) b.
Tuberculosis is no longer the most common cause of Addison's Disease. About 50% of cases are due to corticol atrophy.

(14) b.
The estrogen in the birth control pill is responsible for the hyperglycemia.

(15) b.
Iodine in high concentrations will block oxidization of iodide, but has no effect on the active transport mechanism.

(16) A.
Thyrotoxicosis and Cushing's syndrome are the two most common causes of endocrine myopathy, but myopathy can be seen with all the listed conditions.

(17) D.
Glucagon stimulates glycogenolysis.

(18) D.
Insulin decreases hormone sensitive lipase and antagonizes C-AMP in the adipose cell.

(19) B.
Treatment of adrenal crisis involves replacement of sodium and water as well as administration of glucose. The ideal solution to use is 5% glucose in saline. Hypertonic saline will exaggerate the dehydration of the intracellular space.

(20) D.

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* ILOSONE 250 mg. (erythromycin estolate)

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